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THE AMERICAN JOURNAL
OF THE MEDICAL SCIENCES
MARCH, 1944

ORIGINAL ARTICLES

THE DIAGNOSTIC VALUE OF PANCREATIC FUNCTION TESTS IN 47 SURGICALLY TREATED CASES

By Louis Bauman, M.D.
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NEW YORK, N. Y.

With the technical assistance of
Miss Edith Bratti, A.B., and Miss Paullynn Stines, R.N.

(From the Departments of Medicine and Surgery, Presbyterian Hospital and Columbia University)

Medical men have long been concerned with the motor and secretory abnormalities of the stomach. This organ furnishes pepsin and hydrochloric acid and initiates the digestion of protein. The functional disturbances of the pancreas, however, a gland which supplies protein, starch and fat-splitting ferments, have received scant attention, owing to the lesser accessibility of the organ, and to the lack of a good diagnostic test. The need for a reliable test of the external pancreatic function is obvious when one experiences the difficulty of diagnosis of purely functional disorders as well as cancer and inflammation of this organ.

Secretin, the hormonal stimulant of the pancreas, is a protein compound that can be extracted from the mucous membrane of the small intestine. We are indebted to Hammarsten and collaborators[7] for the preparation of a standardized secretin that is commercially available. The injection of this product into a normal person induces a copious flow of dilute pancreatic juice that is relatively poor in ferments. In acute and chronic pancreatitis Agren, Lagerlof and Berglund[1] found that the pancreatic juice following secretin was low in volume, bicarbonate or ferment concentration or in all 3. Diamond and Siegal[5] on the basis of 130 secretin tests corroborated the results of the Swedish authors and thus confirmed the clinical value of the test.

Neural stimulation of the pancreas through the vagus nerve follows the injection of methyl acetylcholine ("mecholyl"). The resulting juice is more concentrated than that after secretin and therefore richer in ferments.[4]

In pancreatic disease, according to Diamond,[6] the enzyme content of the juice is affected before the bicarbonate concentration. For this reason and because of the difficulty of procuring secretin at the present time our experiences are limited to the use of mecholyl.

The limitations of all functional tests are appreciated. A normal bromsulphalein liver function test is possible when the organ is riddled with carcinoma, provided that normal intervening parenchyma is present. The same applies to kidney tests. The remaining islets suffice to maintain normal dextrose utilization when three-quarters of the human pancreas is ablated.[9] The truisms that no test is 100% reliable and that laboratory results must be correlated with the clinical picture hardly need repetition.

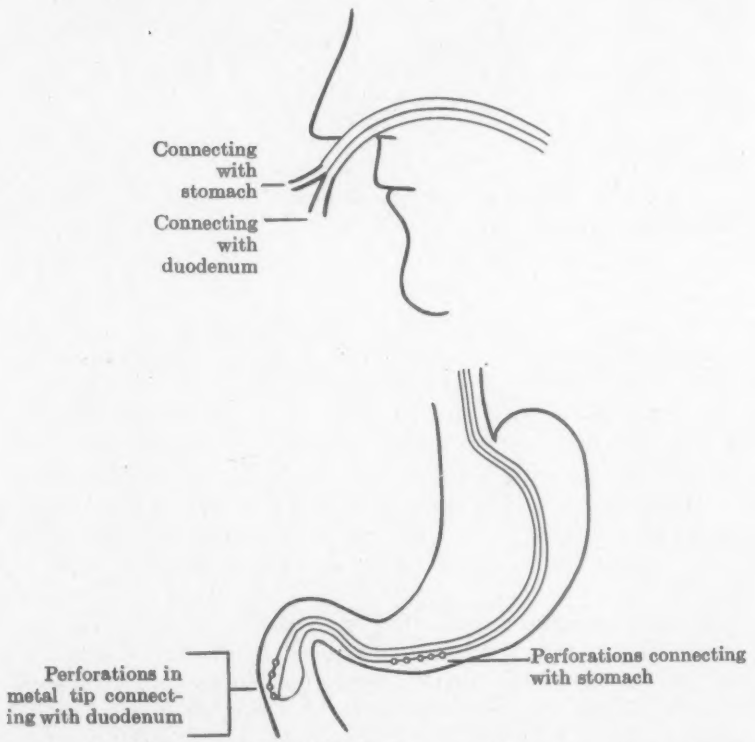
Connecting with stomach
Connecting with duodenum
Perforations in metal tip connecting with duodenum
Perforations connecting with stomach

FIG. 1.—Diagrammatic illustration of removing substance from pancreas.

That disturbance of physiology is not always associated with gross or even microscopic changes is becoming clearer as functional organ studies progress. To quote Professor Virginia Kneeland Frantz,* "In both benign and malignant tumors of islet cells there are no histologic criteria by which we can distinguish those which are functional and those which are not. With an exceedingly small adenoma, a patient may be unconscious from hypoglycemia while with an even larger

* Personal communication.

similar tumor in another case there may be no symptoms of hyperinsulinism."

Recently a middle-aged man with prolonged digestive disturbance and distress in the upper abdomen had normal gall bladder and stomach Roentgen ray reports. He also had achylia gastrica and deficiency of pancreatic ferments yet histologic examination of part of the pancreas removed at operation was normal. It is important to realize that absence or diminution of ferments in the pancreatic juice does not itself signify organic disease of this organ.

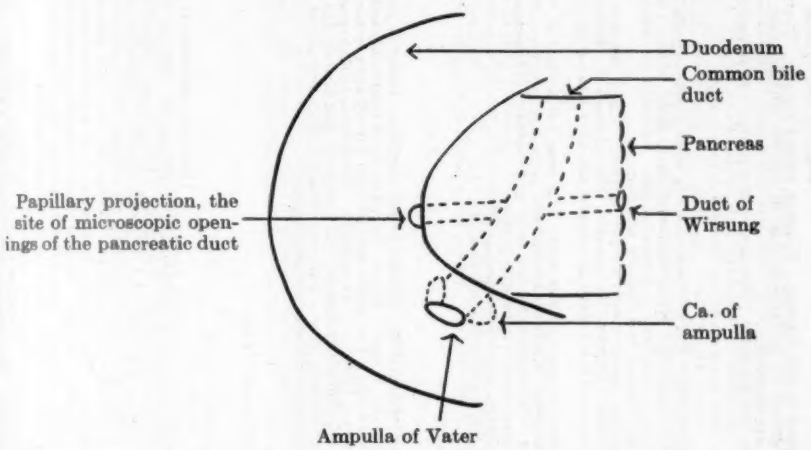

FIG. 2.—Diagram of anatomy of specimen removed at operation. (Case 686471.)

Technique. A rubber tube 4 feet long and 16 French in diameter is used. It is divided into two compartments throughout its length by a central longitudinal partition. One end is provided with a perforated metal tip, the other end projects from the nose where each canal is connected with a short tube. One compartment is perforated at that part of the tube which is in contact with the body of the stomach but has no connection with the duodenum; the other canal is only connected with the duodenum (Fig. 1). The gastric and duodenal secretions can therefore be separately removed by gentle aspiration. Acidification with hydrochloric acid destroys the pancreatic ferments.

After the tube has been passed into the stomach through the nose, the patient is placed on the right side and transported to the fluoroscopy room. The assistance of the roentgenologist* is necessary to manipulate the tube into the duodenum. This is often difficult, time-consuming and at times unsuccessful. Pylorospasm or abnormal conformation of the stomach or duodenum may be the cause of failure. Fifteen mg. of mecholyl are now injected subcutaneously and after 10 minutes the first fraction of pancreatic juice is obtained. Three further 10-minute fractions are collected. Untoward mecholyl effects can be counteracted by atropine. To avoid deterioration of ferments the juice should be collected in tubes immersed in ice-water. If the pH of the fractions is above 7 their ferment activity is determined by the following procedures: Amylase and protease by modified Wohlgemuth and Gross casein methods, respectively,[2] and the lipase by the Cherry and Crandall method.[3]

* We are indebted to Dr. Ross Golden and his staff of the Roentgenology Department of the Presbyterian Hospital for their help.

TABLE 1.—NORMAL FERMENT CONCENTRATIONS OBTAINED IN VARIOUS DISEASES

Hist. No.	Date, 1941	Reaction pH	Fraction	Ferments A	L	P	Serum amylase	Operation	Diagnosis and remarks
563206	...	8.0	a.	+	+	+	20	Yes	Stones in gall bladder. Pancreas looked normal. Typical gall stone history. Pancreas showed no evidence of past or present inflammation. Gall bladder filled with stones was removed.
			b.	+	+	+			
			c.	+	+	+			
449451	10/2	8.0	a.	+	+	+	..	Yes	Chr. cholecystitis. Stones in gall bladder. Pancreas not explored.
			b.	+	+	+			
			c.	+	+	+			
			d.	+	+	+			
657331	10/29	8.0	a.	+	+	+	22	Yes	Gall stones. Stone in common bile duct above ampulla 3.6 cm. Pancreas mostly normal histologically. Some scar tissue about acini. Pain in epigastrium and right upper quadrant. Jaundiced. Cholesterol 685. Bilirubin 19. Phosphatase 7. At operation stone in gall bladder and common bile duct.
664298	1/8/42	7.5+	a.	+	+	+	..	Yes	Painless jaundice with normal ferments. Ca. of common bile duct proximal to ampulla of Vater. Gall bladder palpable. Phosphatase 12. Bilirubin 24. Cholesterol 585. Growth involved lower third of common bile duct but not ampulla.
			b.	+	+	+			
			c.	+	+	+			
			d.	+	+	+			
508263	1/19/42	7.5	a.	+	+	+	39	Yes	Stones in common bile duct. Pancreas felt normal at operation. Man; 60 yrs. Several attacks. Right upper quadrant, pain with jaundice. Bilirubin 9. Amylase 60. Protease 4. At operation—stones in gall bladder and common bile duct. Pancreas slightly edematous. Otherwise normal.
624297	10/22/41	7.7	a.	+	+	+	..	No	Undiagnosed. Normal control.
656238	10/28/41	8.0	a.	+	+	+	..	Yes	Kidney stone. Normal control.
			b.	+	+	+			
660772	11/27/41	7.2	a.	low	0	+	..	Yes	Gall stones.
			b.	+	+	+			
			c.	+	+	+			
638191	4/18/41	7.5	a.	+	+	+	112*	Yes	Chr. cholecystitis. Stones in gall bladder. Pancreas firm and almost nodular. Diabetic curve. Woman; 56 yrs. Long history of indigestion and epigastric pain radiating to shoulder blade. Two weeks ago last attack much more severe. Fever. Leukocytosis. Trace of serum bilirubin. No jaundice. Tenderness in mid-epigastrium. Cholecystogram showed non-filling gall bladder. At operation, gall bladder distended and edematous. No stones in common duct. Pancreas enlarged, firm and almost nodular. Liver normal.
			b.	+	+	+	31*		
658890	1/7/42	7.5	a.	+	+	+	..	No	Undiagnosed condition of abdomen.
			b.	+	+	+			

NORMAL PANCREATIC JUICE

Hist. No.	Reaction of each fraction	Ferments A	L	P	Serum amylase	Operation	Diagnosis and remarks
676458	+7.5	+	+	+	0	Yes	Painless jaundice (obstructive). Inflam. of common bile duct and cirrhosis. Ascites Pancreas histology = normal. Man; 53 yrs. Jaundice (painless). Enlarged liver and spleen. Bilirubin 11.5. Phosphatase 20. Operation, cirrhosis-ascites. Gall bladder not distended; common bile duct not dilated. Induration head of pancreas, but biopsy normal.
		+	+	+			
		+	+	+			
692568	+7.5	+	low	−	..	Yes	Normal pancreas by biopsy. Woman; 47 yrs.; 3 yrs. history of jaundice. Had large liver and spleen. Was anemic, leukopenic, low leukocyte count. Phosphatase 37. Bilirubin 9. Cephalin test, 4+. At oper. liver enlarged, appearance of biliary cirrhosis. Gall bladder small. A hard mass either in second part of duodenum or pancreas. Biopsy of liver: biliary cirrhosis; hard mass: normal pancreas.
	+7.5	+	+	+			
	6.3	+	+	+			
689707	+7.5	+	+	+	11	Yes	Ca. common bile duct verified by biopsy. Female; 47 yrs. Epigastric fullness (10 weeks). Jaundiced. Cholecystostomy. Jaundice continued. Enlarged liver. Glucose tolerance normal. Phosphatase 38.2. Cephalin 0. Bilirubin 12.1. Amylase 12. At operation: ca. of common bile duct involving cystic duct.
	+7.5	+	+	+			
	+7.5	+	+	+			
	+7.5	+	+	+			
685484	+7.5	+	+	+	..	Yes	Ca. bile duct. Female; 52 yrs. Jaundice. Diarrhea. Mass in right upper quadrant. Phosphatase 6.6. Bilirubin 5. Operation: liver enlarged, gall bladder distended; hard mass at junction common and cystic extending up into common hepatic duct and into portal fissure.
	+7.5	+	+	+			
	+7.5	+	+	+			
	6.8	+	+	+			
612668	+7.5	+	low	+	..	Yes	Ca. bile duct. Female; 48 yrs. Jaundice. Bilirubin 8.8. Phosphatase 14.5. Cholesterol 307. Palpable mass right upper quadrant. Operation and pathologic report: cancer of common bile duct.
	+7.5	+	+	+			
	+7.5	+	+	+			
	+7.5	−	−	+			
679967	7.0	+	+	−	..	Yes	Ca. gall bladder. Male; 60 yrs. Epigastric pain through to back. Jaundice. Enlarged
	+7.5	+	+	+			

685484	+7.5	+	+	+	..	Yes	Ca. bile duct. Female; 52 yrs. Jaundice. Diarrhea. Mass in right upper quadrant. Phosphatase 6.6. Bilirubin 5. Operation: liver enlarged, gall bladder distended; hard mass at junction common and cystic extending up into common hepatic duct and into portal fissure.
	+7.5	+	+	+			
	+7.5	+	+	+			
612668	+7.5	+	low	+	..	Yes	Ca. bile duct. Female; 48 yrs. Jaundice. Bilirubin 8.8. Phosphatase 14.5. Cholesterol 307. Palpable mass right upper quadrant. Operation and pathologic report: cancer of common bile duct.
	+7.5	+	+	+			
	+7.5	+	+	+			
	+7.5	−	−	+			
679967	7.0	+	+	−	..	Yes	Ca. gall bladder. Male; 60 yrs. Epigastric pain through to back. Jaundice. Enlarged liver. Bilirubin 17. Phosphatase 15. Operation: cancer of gall bladder.
	+7.5	+	+	+			
	+7.5	+	+	+			
	+7.5	+	+	+			
675458	−4.5	0	low	+	..	Yes	Biopsy pancreas, normal. Biopsy liver, cirrhosis.
	+7.5	+	+	+			
	+7.5	+	+	+			
	+7.5	+	+	+			
467354	−4.5	0	low	low	..	Yes	Ca. hepatic duct. Male; 60 yrs. Jaundice, itching. No pain. Clay-colored stools and enlarged liver with sharp edge. Bilirubin 8.1. Phosphatase 12. G.-I. series and barium enema negative. Pancreatic function test was normal. At operation: ca. of common hepatic duct with collapse of gall bladder. Verified by microscopic examination. Head of pancreas appeared and felt normal. The deleterious effect of acid on the ferments is noticeable.
	+7.5	+	+	+			
	+7.5	+	+	+			
	−4.5	0	+	0			
667435	−4.5	0	low	low	..	..	Normal control.
	7.2	+	+	+			
	7.5	+	+	+			
	7.5	+	+	+			
673800	6.9	+	+	+	..	Yes	Stone in common duct. Pancreas was normal. Male; 70 yrs. 6/3C cholecystectomy and choledochostomy for stone in the gall bladder and common bile duct. Recurrence of pain in epigastrium requiring morphine. Bilirubin 5. Phosphatase 11. Operation: stone in ampulla.
	7.5	+	+	+			
	7.5	+	+	+			
	7.0	+	+	+			
669495	6.7	low	+	+	17	Yes	Negative exploration.
	7.0	high	+	low			
	7.1	high	+	+			
	4.5	0	0	+			
669930	−4.5	0	low	0	..	..	Normal control. Hernia. Illustrating acid effect.
	6.6	low	+	+			
	−4.5	0	low	0			
	−4.5	0	low	0			
671580	−4.5	0	0	low	..	Yes	Ca. head pancreas. Patent pancreatic duct. While tumor surrounded duct, it did not completely obstruct. Female; 58 yrs. Diabetic with painless jaundice of 4½ mos. Enlarged liver. Cholesterol 540. Cephalin 0. Clay-colored stools. Phosphatase 20. Bilirubin 7.5. No bile by duodenal aspiration. Growth in head of pancreas involving uncinate process and common bile duct but not pancreatic duct.
	−4.5	0	0	low			
	+7.5	+	+	+			
	+7.5	+	+	+			
648013	7.1	+	+	+	22	Yes	Lymphosarcoma of peritoneum.
	+7.5	+	+	+			
	+7.5	+	+	+			
	+7.5	+	+	+			
676422	+7.5	+	+	+	..	No	Undetermined.
	+7.5	+	+	+			
	+7.5	+	+	+			
	+7.5	+	+	q.n.s.			
686471	+7.5	+	+	+	..	Yes	Ca. of common bile duct at ampulla. Male; 56 yrs. Severe upper abdominal pain with vomiting and jaundice. Liver large, smooth. Phosphatase 71. Bilirubin 9. At operation, dilated gall bladder. Ca ampulla. Specimen removed (antrum of stomach, duodenum, part of pancreas and dilated common bile duct with tumor at entrance into duodenum): at entrance of pancreatic duct there was a papillary projection, but no opening could be demonstrated, even when probe was inserted into duct of Wirsung. Histologically, this duct divided into numerous microscopic branches, each of which entered duodenum.
	+7.5	+	+	+			
	+7.5	+	+	+			
	+7.5	+	+	+			

* The first serum amylase was determined 16 days and the second 11 days before the enzyme determination in the pancreatic juice.

TABLE 2.—VERIFIED PANCREATIC DISEASE

Hist. No.	Reaction of each fraction	Ferments A	Ferments L	Ferments P	Serum amylase	Operation	Diagnosis and Remarks
639299	7.0+	+	0	0	37	Yes	Ca. of pancreas. Male; 37 yrs. Upper abdominal pain and tenderness. Jaundice. Cholecystojejunostomy. Distended gall bladder. Enlarged pancreas. After operation pain continued. Fatty diarrhea. Glucose tolerance normal. Second operation: hard, firm mass in head of pancreas. Histology: cancer.
		0	0	0			
635632	9.46	0	+	+	228	Yes	Chr. cholecystitis. Stones in gall bladder. Pancreas enlarged, thickened and indurated. No stones in common duct. Female; 34 yrs. Long history of severe epigastric pain radiating to back. No jaundice. Tenderness over epigastrium. High amylase.
652693	7.6	+	0	0	..	Yes	Ca. of pancreas. Male; 68 yrs. Jaundiced. Diarrhea. Bilirubin 20. Phosphatase 25. Operation: growth of head and body of pancreas. Gall bladder distended.
		+	0	0			
		+	0	0			
657473	7.0	low	+	+	44	Yes	Adenoma of islands of Langerhans. Head of pancreas, possibly pressing on pancreatic duct. Male; 49 yrs. Intermittent loss of consciousness. Vertigo. Low blood sugars. Operation: tumor head of pancreas near the common duct. Histology: adenoma or cancer of islands of Langerhans.
697965	5.2	+	low	+	..	Yes	Ca. of pancreas. Male; 60 yrs. One year of fullness of abdomen. Ache around umbilicus. Appetite poor. Jaundiced 3 weeks. Liver and gall bladder palpable. Bilirubin 12.7. Phosphatase 11.7. Cholesterol 437. Operation: prepyloric mass involving common duct and pancreas. Autopsy: ca. head of pancreas with ulceration in stomach and duodenum.
		+	low	low			
		+	low	low			
		0	low	low			
657258	8.0+	+	low	+	22	Yes	Chr. pancreatitis at operation associated with gall stones. Female; 55 yrs. Painless jaundice. Bilirubin 16. Amylase 22. Phosphatase 17. Stones in gall bladder. Common duct enlarged. Head of pancreas showed patchy thickening. Biopsy: pancreatitis.
		+	low	+			
		+	low	+			
700227	7.5+	+	low	0	..	Yes	Ca. head of pancreas involving common bile duct. Male; 73 yrs. Painless jaundice. Large liver. Bilirubin 13. Phosphatase 67. At operation: enlarged gall bladder, large liver. Autopsy: ca. of head of pancreas.
		+	0	low			
		+	0	+			
678265	+7.5	low	low	low	70	Yes	Chronic pancreatitis. Pancreas hard and enlarged. Bilirubin 8.3. Female; 46 yrs. Right upper quadrant pain. Non-filling gall bladder. Later pain in left upper quadrant radiating to back. Jaundiced. W.B.C. 16,100. Bilirubin 8.3. Amylase 70. Operation: stones in gall bladder. Pancreas large and hard.
	+7.5	low	+	low			
	+7.5	low	low				
	+7.5	0	–	low			
692078	+7.5	low	low	+	88	Yes	Infected necrotic cyst of pancreas. Diabetic glucose tolerance curve. Ferments in cyst fluid. Female; 40 yrs. Two months prior to admission epigastric distress, vomiting. Later epigastric pain. Rigidity of epigastrium and tenderness. High serum amylase. Mass in abdomen. Temperature up to 102°. Elevated W.B.C. No jaundice. Roentgen ray: displacement of stomach and duodenum due to enlarged head of pancreas. Operation: abscess of head and body of pancreas. Fluid contained amylase and lipase.
	+7.5	+	low	+			
	+7.5	+	low	low			
687251	4.5	0	low	0	14.5	Yes	Ca. pancreas verified by histologic examination. Diabetic glucose tolerance curve. Male; 39 yrs. Three months pain in back, region of left kidney requiring morphine. Amylase 15. Phosphatase 3.9. No jaundice.
	6.3	0	+	low			
	5.2	0	low	low			
	5.0	0	low	low			
438079	6.0	0	low	0	22	Yes	Chronic pancreatitis confirmed histology. Is a diabetic. Abdominal pain left mid-abdomen. Epigastric fullness, weight loss, slight tenderness right upper quadrant. Bilirubin 6. Phosphatase 20. Amylase 22. At operation gall bladder tense and distended. Large hard pancreas. Section: fibrosis. Repeated pancreatic function test in February 1943 and found no ferments in juice.
	7.5	0	low	low			
	+7.5	0	low	low			
	7.0	0	+	low			
680814	4.6	0	–	–	24	Yes	Chronic pancreatitis. Diabetic glucose tolerance curve. Female; 66 yrs. Belching 2 yrs. Cholecystogram: abnormal. Now jaundice, chills, fever, enlarged liver. Bilirubin 13.8. Phosphatase 17.1. Diabetic glucose tolerance curve. Operation: distended gall bladder. Pancreas hard and nodular.
	+7.5	+	+	low			
	+7.5	+	+	low			
	+7.5	low	low	low			
430645	7.0	low	low	0	..	Yes	Chronic pancreatitis. Stones in gall bladder and common duct. Died of cancer of liver,

	+7.5	0	low	low			Epigastric fullness, weight loss, slight tenderness right upper quadrant. Bilirubin 0. Phosphatase 20. Amylase 22. At operation gall bladder tense and distended. Large hard pancreas. Section: fibrosis. Repeated pancreatic function test in February 1943 and
	7.0	0	+	low			found no ferments in juice.
680814	4.6	0	−	−	24	Yes	Chronic pancreatitis. Diabetic glucose tolerance curve. Female; 66 yrs. Belching 2 yrs. Cholecystogram: abnormal. Now jaundice, chills, fever, enlarged liver. Bilirubin 13.8.
	+7.5	+	+	low			Phosphatase 17.1. Diabetic glucose tolerance curve. Operation: distended gall bladder.
	+7.5	+	+	low			Pancreas hard and nodular.
	+7.5	low	low	low			
430645	7.0	low	low	0	..	Yes	Chronic pancreatitis. Stones in gall bladder and common duct. Died of cancer of liver, metastatic. Pancreas not explored. Had been operated upon by Dr. Whipple for gall
	+7.5	low	low	+			stones and cholangitis, stones in common bile duct.
641333	+7.5	low	low	low	..	Yes	Chronic pancreatitis. Nodular body and tail. Male; 33 yrs. Followed for several years.
	+7.5	+	+	+			Bouts of pain left upper quadrant. Fever and pleurisy with effusion (left). W.B.C. 8600.
	+7.5	+	0	0			Op. elsewhere. Calcified abdominal nodes removed. Roentgen rays of G.-I. tract, 0.
	+7.5	+	low	0			April 1939, gall bladder removed. Blood amylase 43. Operation: nodular tissue behind pancreas, probably chronic pancreatitis. Follow-up: doing well at present time.
679477	−4.5	0	0	0	..	Yes	Cancer of pancreas. Male; 43 yrs. Pain through epigastrium to back for 3 months. Jaundice. Enlarged liver. Phosphatase 23. Bilirubin 8.3. Cholesterol 335. Narrowing of
	7.5	+	low	low			duodenal bulb. Operation: ca. pancreas involving head and body.
	−4.5	0	low	0			
667695	4.5	0	+	+	146	Yes	Acute pancreatitis. Head of pancreas firm. Diabetes. Bilirubin 9.9. Test done 52 days
	7.5	low	+	+			after operation in O.P.D. Diabetic male; 42 yrs. Severe upper abdominal pain chiefly
	+7.5	+	+	+			epigastric lasting 5 days and associated with vomiting. Little tenderness but spasm right
	+7.5	+	low	+			upper quadrant. Bilirubin 9.9. W.B.C. 12,500. Fever. Diagnosis: acute cholecystitis, stones in common duct. At operation gall bladder distended (100 cc.). *No* stones in gall bladder or common duct. Edema of common duct with firm head of pancreas. Path. report: acute cholecystitis. Amylase postoper. 146.
675759	−4.5	0	low	0	30	Yes	Ca. pancreas confirmed by histologic examination. Bilirubin 12. Phosphatase 11.4. Male;
	+7.5	+	low	0			60 yrs. Pain in back level 12 T vertebra. Later jaundiced. Enlarged liver. Cholecys-
	+7.5	+	low	+			tectomy at another hospital. Diarrhea. Bilirubin 10.6. Phosphatase 7.6. Operation:
	−4.5	0	low	low			induration head of pancreas. Biopsy: ca.
686760	+7.5	low	low	+	..	Yes	Ca. head of pancreas without jaundice. Male; 83 yrs. Vomiting for 1 yr. Roentgen ray:
	+7.5	low	low	+			obstruction third part of duodenum. Operation: ca. head of pancreas without jaundice.
	+7.5	low	low	+			
	+7.5	low	low	+			
689412	+7.5	low	+	+	33	Yes	Cyst attached to tail of pancreas. Biopsy: neurolemoma. Glucose tolerance normal. Cyst
	+7.5	+	+	+			(in left abdomen, below costal margin). Arose from region of tail of pancreas, adherent
	+7.5	+	low	low			to aorta. Pathologic diagnosis: neurolemoma.
	+6.0	+	low	low			
678490	+7.5	low	+	+	53	No	Following cholecystectomy for gall stones. Five years of attacks epigastric pain radiating to
	+7.5	low	+	low			back. Cholecystectomy 16 years ago for gall stones. Pancreas not explored. One week
	+7.5	low	+	low			after operation epigastric pain radiating to left shoulder. Nine, 8 and 7 years ago bouts of
	+7.5	low	+	low			epigastric pain. On admission, epigastric pain, vomiting, weight loss. Bilirubin 6.4.
							Amylase 53. Phosphatase 11. Is being followed without op. Diagnosis: chronic pan-
							creatitis. Diabetic glucose tolerance test.
543316	−4.5	low	−	0	48.7	Yes	Chronic pancreatitis. Induration head pancreas. Male; 38 yrs. In 1937, crampy epigastric
	7.5	low	+	0			pain radiating to back with 2 subsequent attacks, the last with fever, epigastric rigidity
	6.4	low	+	0			and tenderness. W.B.C. 28,000. Amylase 73. Bilirubin 5. At operation: stones in gall
	5.0	low	+	0			bladder and common duct. Pancreas large and firm. Cholecystectomy and drainage of
							common bile duct. 8/39, attacks of epigastric pain through to back. Tender L. epig. Amy-
							lase 95. Bilirubin 1. 4/40, L.U.Q. pain. 11/40, readmission, R. and L.U.Q. pain. Opera-
							tion: indurated head of pancreas. Choledocho-duodenostomy. No stones. 4/41, recur-
							rence of pain R.U.Q. 1/42, amylase 49. Operation: hard lumps in pancreas. Plastic
							on ampulla. 10/42, recurrence of attacks.

TABLE 2.—VERIFIED PANCREATIC DISEASE—*Continued*

Hist. No.	Reaction of each fraction	Ferments A	Ferments L	Ferments P	Serum amylase	Operation	Diagnosis and Remarks
668231	5.0	low	low	+	25	Yes	Ca. of pancreas. Weight loss. Vomiting. Sharp lower abdominal pain for 3 mos. Phosphatase 9. No jaundice. Operation: ca. pancreas with liver involvement.
	6.9	0	+	low			
	6.9	0	0	low			
	4.5	0	0	low			
673028	4.5	0	low	0	..	Yes	Chronic pancreatitis. Ca. of pancreas. Glucose tolerance diabetic. Male; 56 yrs. 7/1/41, sharp epigastric pain. Later jaundice. Bilirubin 4. No anemia. (1) Operation (8/7/41): distended normal gall bladder. Entire pancreas enlarged, hard and fibrous. Pathologic report: fibrosis. Cholecystjejunostomy. (2) Operation 4/13/42: choledochojejunostomy-cholecystectomy. Head and body of pancreas swollen and hard. Two large sections showed only fibrosis. Prev. cholecystjejunostomy was not functioning. He absorbed 86% of ingested fat. Pain severe, continued. (3) Operation 8/3/42: revealed ca. of ampulla. Probable ca. of ampulla with pancreatitis.
	7.5	low	low	0			
	7.5	low	low	0			
	−4.5	0	0	0			
671069	−4.5	0	0	0	..	Yes	Ca. of pancreas. Male; 76 yrs. Six to 8 months mild epigastric pain and fullness, anorexia, jaundice. Mass in right upper quadrant. Bilirubin 22. Phosphatase 14. Cholesterol 369. Operation: large indurated mass involving head of pancreas. Distended gall bladder.
	−4.5	0	0	+			
	−4.5	0	0	+			
	−4.5	0	0	+			
672681	7.2	low	low	low	31	Yes	Marked fibrosis and calcification. Diabetic glucose tolerance curve. Chronic pancreatitis in Roentgen ray with calcification seen. Male; 48 yrs. Five to 6 years of abdominal pain going through to back. One attack associated with jaundice. Operation: cholecystectomy of a gangrenous inflamed gall bladder. Recurrence of pain. Roentgen ray showed calcification of the pancreas. Diabetic glucose tolerance curve. Pancreatic duct sewed into jejunum. Good follow-up January 9, 1943.
	+7.5	low	low	low			
	+7.3	low	low	low			
	−4.5	0	low	0			
671642	+7.5	0	+	+	61	Yes	Chronic pancreatitis with stones in pancreatic duct. Male; 42 yrs. Vague digestive symptoms. Pain in epigastrium through to back. Abdominal distention. Cholecystogram, barium enema, G.-I. series negative. During attack spasm mid-epigastrium. Elevated W.B.C. Amylase 49. No abnormal calcification in region of pancreas. Amylase 61. No jaundice. Operation: no distention of gall bladder or common bile duct. Hard edematous head of pancreas thought to be malignant. Calcification when cut. Histology: pancreatitis, pancreaticolithiasis. Diabetic glucose tolerance curve. Follow-up 2/3/43: doing well.
	+7.5	0	+	low			
	+7.5	0	+	low			
	+7.5	0	+	low			
701945	−4.5	0	+	0	54	Yes	Pancreatic involvement by perforated peptic ulcer. Male; 56 yrs. Seven years of pain in right upper quadrant, epigastrium and lower abdomen radiating to chest and back. Occasional vomiting. Cholecystogram: normal. G.-I. series: ulcer pyloris. At operation pyloric or duodenal ulcer perforating into the head of pancreas.
	+7.5	+	low	0			
	+7.5	+	low	0			
	5.0	low	+	+			

Results. We have divided the cases into 2 groups, those with normal ferment concentrations and those with abnormal ferment concentrations due to proven pancreatic disease.

Normal Results (Table 1). It is apparent that in cases of stone in or cancer of the bile ducts, normal pancreatic juice is usually obtained. Painless obstructive jaundice associated with normal pancreatic juice is usually found in cancer of the bile ducts. In tumor of the ampulla normal pancreatic ferments may be obtained if the pancreatic duct or ducts enter the duodenum separately, or if there is an accessory duct of Santorini.

Figure 2 is a diagram of the anatomy of the specimen removed at operation from Patient 686471. Grossly the tumor at the ampulla was easily demonstrable but the entrance of the pancreatic duct could not be found though normal pancreatic ferments had been obtained. Microscopic examination revealed minute branches of the duct of Wirsung entering the duodenum.

In only 1 patient (No. 671580) with proven cancer of the pancreas were normal ferments obtained. In this case there was a cancer of the head of the pancreas invading the common bile duct without obstructing the pancreatic duct.

In the series with normal pancreatic ferments no evidence of pancreatic disease was found except in Case 657331, where the histology of a biopsy specimen showed a predominantly normal picture with an occasional patch of fibrosis.

Patient 638191 had a serum amylase that was elevated to about 3 times the normal level, a diabetic glucose tolerance curve but normal concentrations of ferments in the pancreatic juice. The surgeon found the pancreas firm and almost nodular to palpation.* The serum amylase tests preceded the pancreatic function test by about 2 weeks.

Patient 508263 with stones in the common duct had been observed for 5 years but had steadfastly refused operation before. The possibility of pancreatitis was considered but with normal ferments this supposition was considered unlikely. At operation 7 stones were found in the common duct. The pancreas felt normal.

Results in Pancreatic Diseases (Table 2). Painless obstructive jaundice with low or absent pancreatic ferment concentration is almost always due to cancer of the pancreas. Pancreatitis is usually associated with pain and if acute an elevated serum amylase is the rule. The determination of serum amylase has become one of the important clinical laboratory procedures. An elevated serum amylase is a reliable indication of acute pancreatic disease. This ferment is readily excreted by the kidney so that a fleeting edema of the pancreas may escape recognition if the test is delayed.

It is noteworthy that alkaline juice is usually present even in advanced pancreatic disease and that the activity of the 3 ferments is not affected to the same extent. In some patients the concentration of 1 ferment remains normal while that of the other 2 is markedly diminished.

* Deductions drawn from the feel of the pancreas at operation have proven erroneous in a number of cases.

Summary. The reaction and ferment concentration of the pancreatic juice has been determined in about 150 patients.

This experience, together with that of Pratt[8] of Boston and the other clinicians already quoted, indicates that a test of the external function of the pancreas may well become an important diagnostic procedure.

Conclusions. Mecholyl injection induces the secretion of a relatively concentrated pancreatic juice which is well adapted for ferment determination.

Separate aspiration of the stomach is necessary to avoid acidification which injures the pancreatic ferments. A tube with 2 lumina is used for this purpose.

Functional disturbances of the external secretion of the pancreas may occur without demonstrable histologic changes in the organ.

Painless obstructive jaundice with normal pancreatic ferments favors the diagnosis of carcinoma of the bile duct. In tumor of the ampulla, normal ferments may be obtained if the pancreatic duct enters the duodenum separately or if there is an accessory duct of Santorini.

Painless obstructive jaundice with diminished or absent ferments favors the diagnosis of carcinoma of the pancreas.

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THE EFFECTS ON EXPERIMENTAL TUBERCULOSIS OF 4,4′-DIAMINODIPHENYLSULFONE

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At the present time the chemical agents that have proved most effective in combating experimental tuberculosis of guinea pigs have been derivatives of 4,4′-diaminodiphenylsulfone.[1,4,7,8,13,15] Although a fairly large number of derivatives of this compound have been subjected to tests *in vivo* to determine their possible effects on tuberculosis

induced experimentally, relatively few experiments have been reported concerning the ability of 4,4′-diaminodiphenylsulfone to influence an experimental tuberculous infection.

Rist, Bloch and Hamon,[14] in 1940, reported on the effect of 4,4′-diaminodiphenylsulfone on rabbits and guinea pigs inoculated intravenously with avian tubercle bacilli. Since peroral administration of the drug in the dose employed induced in rabbits considerable and serious toxic manifestations, the rabbits received the drug subcutaneously suspended in olive oil. The drug, mixed with mucilage of tragacanth and syrup, was given by mouth to the guinea pigs. Although the experiments were of relatively short duration the results, based on the number of tubercle bacilli in the lesions and the histologic character of the tissue changes, indicated that a definite inhibitory effect had been achieved.

In 1942 Smith, Emmart and Westfall[15] studied the effects of several compounds, including 4,4′-diaminodiphenylsulfone, on experimental tuberculosis of the guinea pig. Although histopathologic studies were not reported, they stated that of the several drugs that exerted a deterrent effect on experimental tuberculous infection 4,4′-diaminodiphenylsulfone was the most effective. Smith, Emmart and Westfall emphasized the toxic nature of this drug but in view of its high specificity they expressed the belief that the search for more effective and less toxic derivatives should provide a promising field of investigation.

The Drug. 4,4′-Diaminodiphenylsulfone is a drug of unusual interest and importance because of the possibility that some previously reported tuberculotherapeutic drugs ("promin"* and diasone† may break down in the body to diaminodiphenylsulfone or a similar substance common to all. There is no proof that such breakdown occurs, but the union between the parent substance and the added radicals would appear to be unstable. Experience has shown that promin has quite different effects when given orally than it has when given parenterally, suggesting that some significant chemical transformation occurs in the digestive tract.

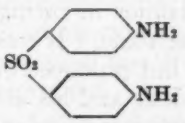

FIG. 1.—Structural formula of 4,4′-diaminodiphenylsulfone.

4,4′-Diaminodiphenylsulfone, which we obtained through the kindness of Dr. E. A. Sharp and Dr. L. A. Sweet, Parke, Davis & Co., Detroit, Mich., is somewhat simpler in chemical constitution than are most of the more popular chemotherapeutic compounds. The structural formula assigned to this compound is illustrated in Figure 1. As may be noted, 4,4′-diaminodiphenylsulfone is not a sulfonamide

* Sodium p,p′-diaminodiphenylsulfone-N,N′-didextrose sulfonate.
† Sodium formaldehyde sulfoxylate diaminodiphenylsulfone.

derivative, as are most of the widely used products available at this time. The diphenylsulfone nucleus of this substance is the essential feature of the so-called "sulfone" group of compounds which sharply distinguishes them from the "sulfonamide" group of compounds. It is important to emphasize the distinction between these 2 groups of substances because of increasing evidence that the therapeutic and toxic effects are quite different and contrasting in the 2 instances. Significant tuberculotherapeutic effects are essentially lacking in the sulfonamide series but are present in striking degree in several compounds of the sulfone series. There are differences in the toxic effects of the 2 groups of substances and their absorption, excretion, detoxication and mode of action may be quite different, but the latter have been inadequately studied.

Diaminodiphenylsulfone, which has a molecular weight of 248, is quite insoluble in water at room temperature (0.01%). Its crystals are described as long, rectangular, colorless flakes that have a melting point of 176° C. It has little taste and may be mixed with the feed of animals without impairing palatability. In mice, toxic doses of the drug cause the animals to become agitated and restless in behavior, undoubtedly a neurotoxic effect. Incidentally, sulfanilamide is also a neurotoxic drug for mice but produces paralysis rather than excitement and stimulation. Diaminodiphenylsulfone is absorbed rather slowly from the gastro-intestinal tract, and the presence of the compound in the blood stream persists for a much longer period than in the case of sulfanilamide and related substances. Long and Bliss[12] stated that "its acute toxicity is so great as to preclude its use in clinical therapeutics." However, Long and Bliss did not present the evidence on which this conclusion was based. No adequate study of the effects of this compound on the human being has come to our attention.

4,4′-Diaminodiphenylsulfone was first synthesized by Fromm and Wittmann[11] in 1908, but the drug did not find any practical application until 1937 when Buttle, Stephenson, Smith, Dewing and Foster[3] discovered its remarkable efficacy in treatment of experimental streptococcal infections of mice. They noted that this compound was much more effective than sulfanilamide in curing streptococcal infections of mice but likewise it was more toxic. It was much less toxic for rabbits and monkeys than for mice but produced methemoglobin more readily than did sulfanilamide. Buttle and his associates found that when a single dose of 0.3 gm. was given to a man his blood became bactericidal for streptococci. Fourneau, Tréfouël, Nitti, Bovet and Tréfouël[9] made similar observations while working independently with this drug at the same time.

Bauer and Rosenthal,[2] in 1938, reported that 4,4′-diaminodiphenylsulfone was about 30 times as effective as sulfanilamide against streptococci. They found the therapeutic index* to be 6, compared with an index of 3.3 for sulfanilamide and 20 for diacetyldiaminodiphenylsulfone. No extensive effort at clinical application of these findings

* The therapeutic index was determined by Bauer and Rosenthal[2] by dividing the maximal tolerated dose by the minimal effective dose.

had been reported, doubtless because of the toxic potentialities of the drug.

4,4′-Diaminodiphenylsulfone has also been found to be distinctly superior to sulfanilamide in curing mice of pneumococcal infections.[3,10]

Methods. The report that follows is based on data from 3 separate experiments. In all instances young adult male guinea pigs whose average weight was approximately 450 gm. were used. The feed consisted of so-called rabbit chow to which was added corn syrup supplemented twice weekly with fresh cabbage. The infecting agent was a human tubercle bacillus, strain H37RV, grown on the synthetic medium of Proskauer and Beck. The animals were caged in pairs. The drug was mixed with the feed to the amount of 0.33% by weight.* The daily intake of the drug was estimated to be approximately 150 mg. per animal.

Experiment 1. Twenty-eight animals were utilized. These were divided into 2 groups of 14 guinea pigs each. Two days before the animals were inoculated with tubercle bacilli the drug was added to the feed of 1 group. Forty-eight hours later each animal in both groups was inoculated subcutaneously in the sternal region with 0.1 mg. of an 18-day-old culture of tubercle bacilli (H37RV). Administration of the drug with the feed was continued daily, and the experiment was terminated on the 60th day after infection.†

Experiment 2. Two groups of 10 guinea pigs each were selected. The experimental procedure followed was essentially the same as that described for experiment 1.‡ The experiment was terminated 60 days after inoculation with tubercle bacilli.

Experiment 3. Forty-two guinea pigs were used. Each was inoculated subcutaneously in the sternal region with 0.0005 mg. of a 23-day-old culture of H37RV.

Forty-two days later all of the guinea pigs were found to be sensitized to tuberculin.§ At this time the animals were divided into 2 groups. Group 1 consisted of 28 animals; these were the untreated controls. Group 2 consisted of 14 animals; these were treated with 4,4′-diaminodiphenylsulfone. (Treatment was thus begun 6 weeks after the animals received the infective dose.) The experiment was continued for 228 days after the animals had received the infective inoculum. The animals in the treated group had received the drug for a total of 186 days. When the experiment was terminated, the animals that were living, in both groups, were killed.

Results. *Comparative Survival Times.* In Experiment 1, in which there were 14 animals in each group (treated and untreated), only 1 guinea pig had died when the experiment was terminated on the 60th day. The 1 death occurred in the group that was being treated. The animal died 35 days after inoculation with tubercle bacilli and had received 4,4′-diaminodiphenylsulfone for a total of 37 days. The cause of death was not determined. Since only 1 animal in the treated group died and all of the untreated ones lived, the difference in the survival time of the animals in the 2 groups appears to be of no significance.

* This dose was selected after feeding trials and represents an approximate molecular equivalent to 3 times as much promin. The molecular weight of promin is 780 while that of 4,4′-diaminodiphenylsulfone is 248.

† Details concerning the feeding of guinea pigs in experiments pertaining to chemotherapy of tuberculosis and information regarding the strain of tubercle bacilli used (H37RV) and its cultivation have been published previously.[7]

‡ In Experiment 2, the age of the culture was 20 days.

§ Gilleland's OT diluted 1:100. Each animal received 0.02 to 0.03 cc. intracutaneously.

In Experiment 2, in which there were 10 animals in each of the 2 groups, 2 guinea pigs died during the 60-day period of observation. Both animals that died belonged in the group that was being treated. The first animal died on the 22nd day and the second on the 55th day after inoculation. In each instance the cause of death was not apparent.

In the third experiment 20 of the 28 (71.4%) animals in the untreated group died before the end of the observation period (228 days after infection) while in the group that had been treated 10 of 14 (71.4%) were living 228 days after inoculation (Fig. 2). The first death among the untreated controls occurred on the 92nd day after

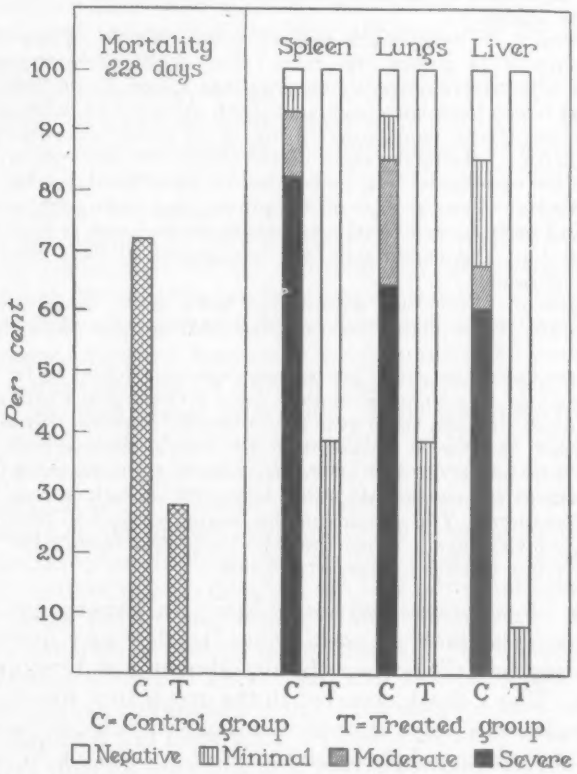

FIG. 2.—Relative mortality rates and amounts and character of tuberculosis in treated and in untreated guinea pigs (Experiment 3).

infection and with one possible exception each of the 20 animals in this group that died had a sufficient amount of tuberculosis to have been responsible for death. The 4 deaths among the animals that were receiving 4,4′-diaminodiphenylsulfone occurred on the 47th, 78th, 88th and 111th day after infection, respectively. Tuberculosis was the obvious cause of death of the animal that died on the 47th day. The disease was severe in the spleen and lungs and moderate in the liver. This animal had received treatment for 5 days only. The cause of death of the other 3 animals in the treated group that died before the experiment was terminated was not determined. Each of the 3

guinea pigs was tuberculous, but the disease was minimal and presumably not sufficient to account for death.

In the first 2 or short-term experiments, since none of the controls died during the 60-day period of observation and 3 deaths occurred among the animals receiving 4,4′-diaminodiphenylsulfone, one may presume that the animals died from the toxic effects of the drug. This is a presumption only, since objective signs indicative of toxicity were not observed. From the point of view of therapeutic efficacy the mortality rate is of no value in an experiment of 60 days duration when the infective agent is introduced into the subcutaneous tissues. Even though excessively large amounts of the infective inoculum be used, 60 days is too short a period to expect any considerable number of untreated controls to die. In a short-term experiment evidence of therapeutic effect must be sought in the amount and character of the tuberculosis in the respective animals.

In the third experiment the observations were continued for a sufficiently long period to make the relative mortality rates of the treated and untreated groups of some significance. The results as given previously indicate quite definitely that as a whole the group that was treated lived a great deal longer than the group that was not treated. It is of interest to note that of the 4 treated animals that died, the death of the last of the 4 occurred 111 days after the animal had received the infective inoculum, whereas 16 (80%) of the 20 animals of the control group that died did so after this time. These data suggest the favorable influence of therapy in prolonging the survival time of the animals in the group that were treated.

Relative Amounts of Tuberculosis in Treated and Untreated Groups. Of much interest and importance in determining the effect, if any, of a chemical agent administered with therapeutic intent to tuberculous guinea pigs are the amount and character of the tuberculosis in the treated and untreated groups of animals. With drugs having little, if any, deterrent effect on the disease process sufficient information can usually be obtained by comparing the gross changes in the organs of predilection of the treated and untreated animals. However, in instances in which the gross examination suggests or indicates that the therapeutic agent has exerted a favorable effect on the expected course of the disease, a proper evaluation of the influence of the drug is possible only by a microscopic examination of the tissues. This is especially true in relatively short-term experiments in which there is insufficient time for the disease to express its maximal severity. Microscopic studies will frequently reveal residual disease or relics of previous disease that could not have been detected grossly. One should not be satisfied with less exacting criteria.

Following a scheme which has been described previously,* a sum-

* This scheme for evaluating numerically the relative severity of tuberculosis in experimentally infected guinea pigs is based on (1) the premise that a non-progressive or arrested tuberculous process should be assigned a value inferior to that assigned to processes that are progressive and destructive and (2) on the arbitrary selection of the figure 100 as representing the maximal amount of tuberculosis possible in any one animal. A detailed description of the scheme and of its application has been reported previously.[5]

mary of the effects of 4,4′-diaminodiphenylsulfone in the respective experiments is given in Table 1.

TABLE 1.—SUMMARY OF THE EFFECTS OF 4,4′-DIAMINODIPHENYLSULFONE EXPRESSED NUMERICALLY

(All animals were inoculated subcutaneously with H37RV. The dose of the inoculum in Experiments 1 and 2 was 0.1 mg. In Experiment 3, the dose was 0.0005 mg.)

Experiment	Duration (days)	Group	Numerical index of infection determined microscopically: Spleen (Max. 35)	Lungs* (Max. 30)	Liver (Max. 25)	Site of inoculation* (Max. 10)	Average index (Max. 100)
1†	60	Control (14 animals)	31.8	16.4	18.2	10.0	76.4
		Treated (13 animals)	1.3	1.7	1.3	7.8	12.1
2†	60	Control (10 animals)	26.1	19.0	16.3	10.0	71.4
		Treated (10 animals)	2.9	3.8	1.2	6.4	14.3
3‡	228	Control (28 animals)	31.3	24.7	18.4	9.7	84.1
		Treated (13 animals)	1.4	2.8	0.23	4.0	8.4

* Includes contiguous lymph nodes.
† Administration of drug started 2 days prior to infection.
‡ Administration of drug delayed until 42 days after infection.

It may be noted that in the 2 experiments that were terminated 60 days after infection, the average index of infection among the animals that were not treated was 76.4 and 71.4, respectively, whereas for the animals that received the drug the average index of infection was considerably less, being 12.1 and 14.3 respectively. These differences, indicative of a deterrent effect of the drug, become even more impressive if the involvement of the spleen, lungs and liver only is considered and the disease at the site of inoculation is disregarded. With these limitations the figures for Experiment 1 would be: untreated group 66.4,* treated group 4.3; for Experiment 2 the average numerical index for the untreated group would be 61.4 and for the group that was treated, 7.9.

The differences in the indexes of infection were most striking among the 2 groups of animals utilized in the long-term experiment (No. 3). Among the untreated controls the average numerical index of infection was 84.1 (based on an arbitrary maximum of 100), whereas in those animals that received the drug the average numerical index of infection was only 8.4. If one disregards the involvement at the site of inoculation and the contiguous lymph nodes, the figure for the untreated group is 74.4 compared with 4.4 for the group that was treated.*

Of considerable significance was the observation that among the 13 guinea pigs treated with 4,4′-diaminodiphenylsulfone in Experiment 3, 6 (46%) were devoid of lesions of tuberculosis—grossly and microscopically—in the liver, spleen and lungs. In contradistinction to the findings just mentioned there was only 1 among the 28 animals that were not treated, in which lesions, although present at the site

* If the site of inoculation is disregarded the maximal index is 90 instead of 100.

of inoculation and in contiguous lymph nodes, were not demonstrable in the liver, spleen or lungs.

Pathologic Changes. Aside from those animals that were treated with 4,4′-diaminodiphenylsulfone and were without lesions of tuberculosis in the organs of predilection (Experiment 3) the most impressive indication that the drug was capable of a tuberculotherapeutic effect was the difference in the histopathologic characteristics of the tissues of the treated and of the untreated animals.

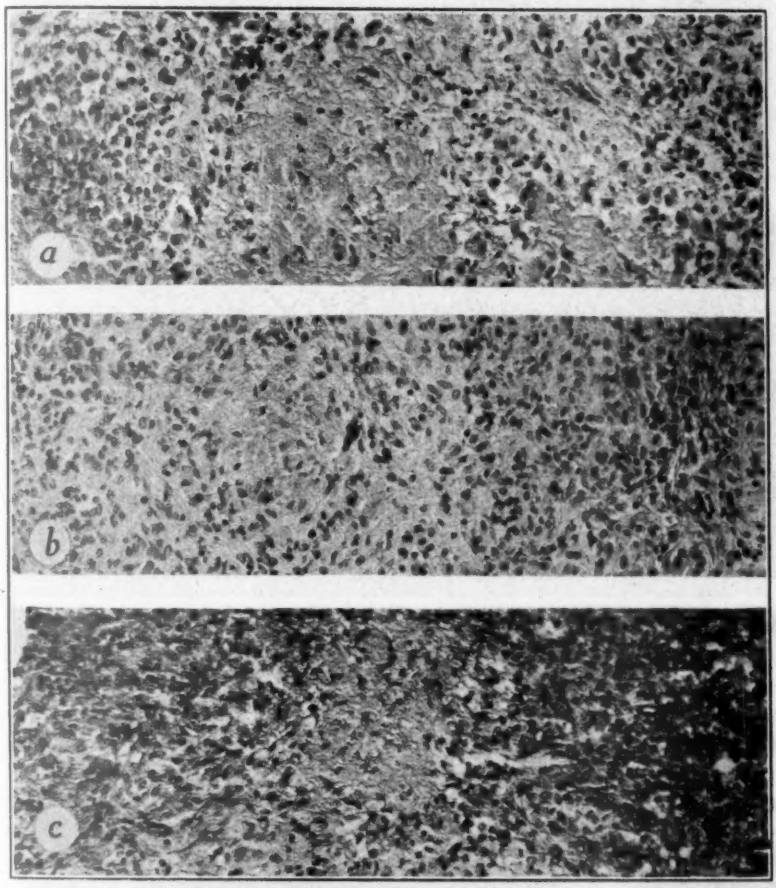

FIG. 3.—Progressive destructive tuberculous changes in (*a*) spleen, (*b*) liver and (*c*) lung of an untreated guinea pig killed 60 days after infection (Experiment 1) (× 150).

In Experiments 1 and 2 the aggressive character of the disease in the untreated controls was in sharp contrast to the physical characters of the disease among the animals that had received the drug. In the former the liver, spleen and lungs were involved moderately or extensively with necrotizing, disseminating and destructive tuberculosis (Fig. 3). When lesions were present in the liver, spleen or lungs of the animals that had received 4,4′-diaminodiphenylsulfone, they were

definitely of a different character from the morbid process that characterized the lesions in the untreated controls. Among the treated

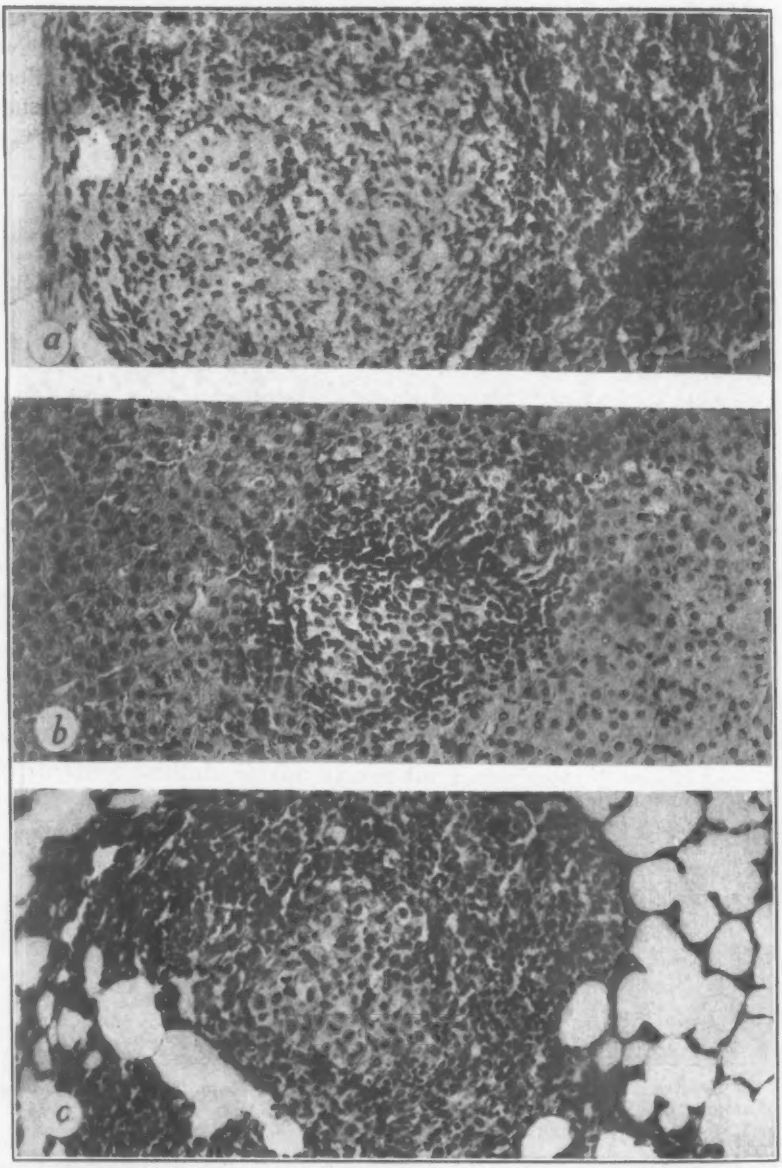

FIG. 4.—Non-progressive tuberculous changes in (*a*) spleen, (*b*) liver and (*c*) lung of a guinea pig that received 4,4′-diaminodiphenylsulfone for 60 days after infection was established (Experiment 1) (× 150).

animals the tuberculous changes of the liver, spleen and lungs were usually focal rather than diffuse and the lesions were relatively few and small. Necrosis was infrequently observed and, when present,

was minimal in amount. The tubercles were often of the so-called hard variety or the epithelioid cells showed retrogressive changes as a

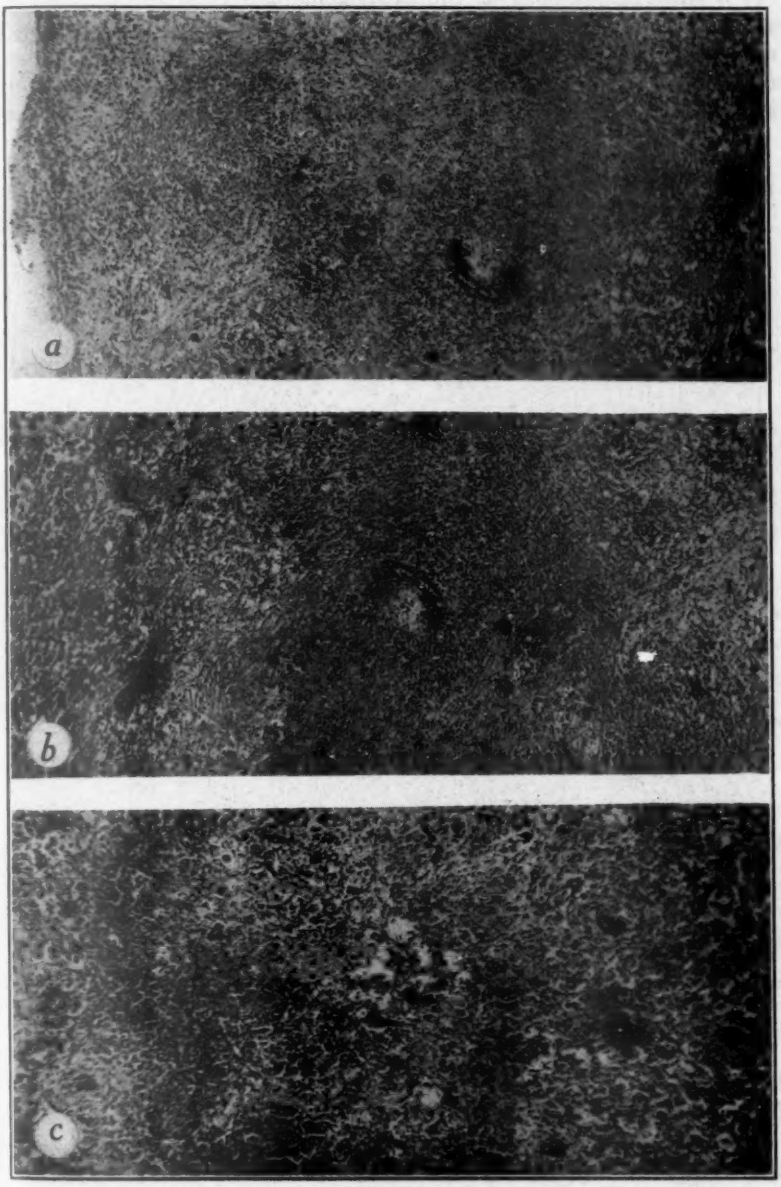

FIG. 5.—Extensive necrotizing tuberculous involvement in (*a*) spleen, (*b*) liver and (*c*) lung of an untreated guinea pig. The animal was killed 228 days after infection (Experiment 3) (× 60).

consequence of which "foam cells" were numerous. A moderate to an intensive accumulation of lymphocytes and histiocytes occurred at the periphery of many of the lesions (Fig. 4).

The pathologic changes that occurred in both groups of animals in Experiment 3 were more dramatic than those of Experiments 1 and 2. The duration of the infection in Experiment 3 (228 days) provided (1) a fuller expression of the pathogenic potential of the infectious agent in the untreated group, and (2) a greater length of time for the drug to exert a favorable influence among the animals that were treated. Parenthetically, it should be recalled that the beginning of treatment in Experiment 3 was delayed until 6 weeks after the animals

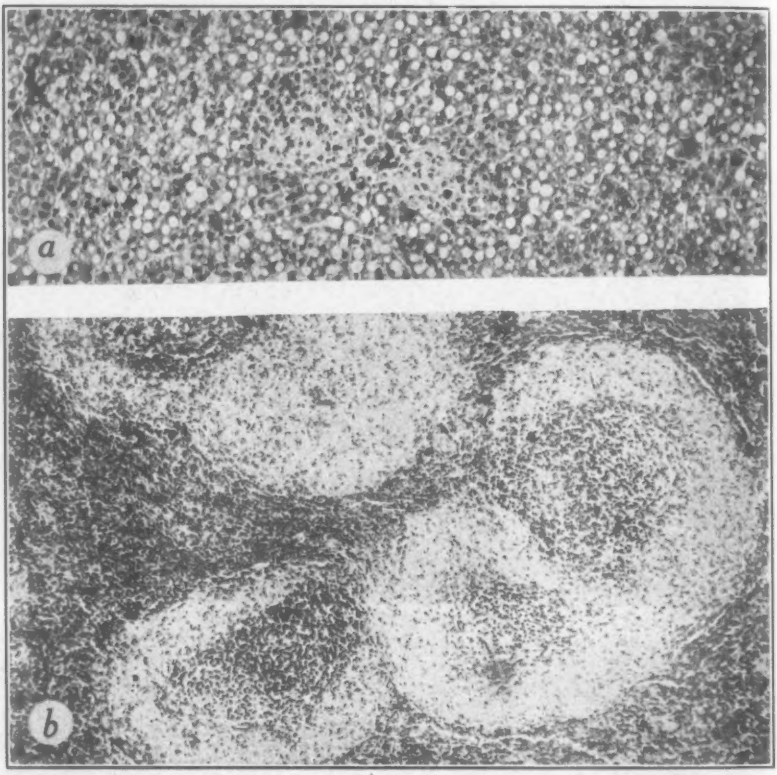

FIG. 6.—(*a*) Atrophic epithelioid nodules in the liver of a tuberculous guinea pig treated for 69 days with 4,4′-diaminodiphenylsulfone (× 100). (*b*) Fibroblastic changes of splenic lesions indicative of healing. The animal died after receiving 4,4′-diaminodiphenylsulfone for 34 days (× 75).

had been infected. This fact might be expected to militate against favorable therapeutic effects of the drug.

The histopathologic character of the disease in the untreated animals was that of an apparently uninhibited process that had succeeded in many instances in occupying much, if not most, of the respective organs of predilection. Necrobiosis was a constant and striking feature, and in some instances the parenchymal involvement was so severe as to obliterate identifying histologic "landmarks" (Fig. 5).

Among the animals in Experiment 3 treated with 4,4′-diaminodi-

phenylsulfone for 186 days, as mentioned previously, there were relatively few of the organs of predilection in which residual lesions of tuberculosis could be found. In the one liver in which lesions were seen they consisted of 2 small atrophic epithelioid nodules which were evidently non-progressive, since the animal had been infected 111 days prior to death, having been treated the last 69 days of life (Fig. 6*a*). The changes observed in the spleen of 1 animal that died after having received treatment for 34 days were of some interest because of the

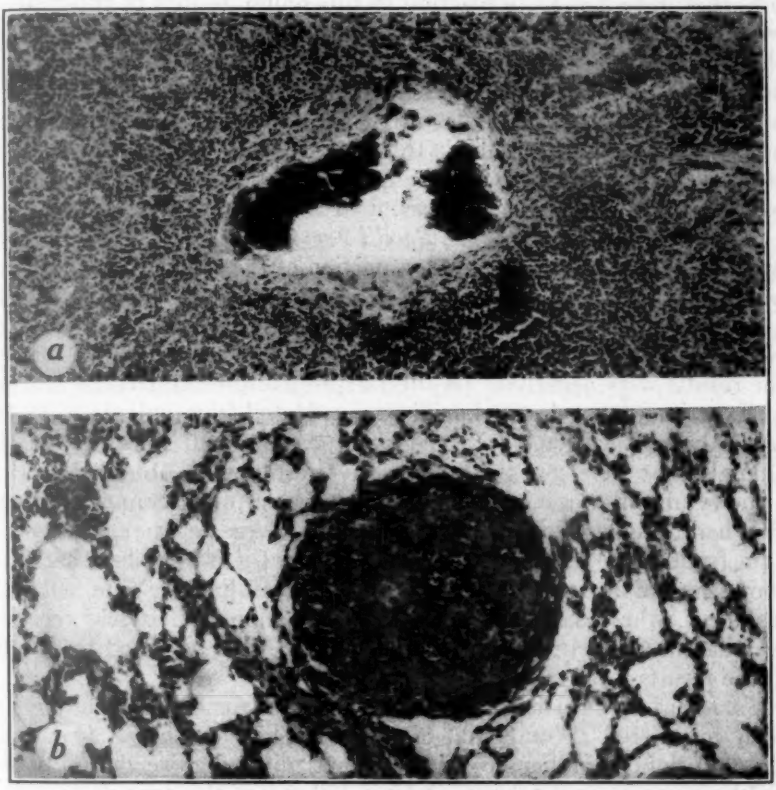

FIG. 7.—(*a*) Calcified nodule in spleen of a tuberculous guinea pig treated for 186 days with 4,4′-diaminodiphenylsulfone. This was the only lesion found in the organs of predilection in this animal (× 100). (*b*) Solitary "hard tubercle" in the lung of a guinea pig treated for 186 days with 4,4′-diaminodiphenylsulfone (× 100).

marked fibrosis of what were presumed to be tuberculous changes (Fig. 6*b*). The 2 spleens that contained lesions among the 10 guinea pigs that were killed when the experiment was terminated showed only a few well-encapsulated calcified nodules (Fig. 7*a*). The lesions observed in the lungs were few and consisted of "hard tubercles" (Fig. 7*b*). A finding worthy of mention was an apparent tendency of the lesions of the axillary lymph nodes of the treated animals to calcify.

Sensitivity to Tuberculin. Two days before Experiment 3 was terminated the animals that were living were again inoculated with tuberculin intracutaneously. Of the 8 untreated animals tested the results in 6 were definitely positive, in 1 negative and 1 animal died before the test was completed. Each of the 8 animals was extensively tuberculous. Of the 10 guinea pigs that had received 4,4′-diaminodiphenylsulfone for 186 days and which were sensitized to tuberculin when the treatment was started, the results were as follows: 5 definitely positive, 2 indefinitely positive and 3 negative. Of the 5 guinea pigs that gave a definite reaction to tuberculin, lesions of tuberculosis were present in the organs of predilection of only 1. Of the 2 in which the reaction to tuberculin was indefinite, lesions of minimal and non-progressive character were present in the spleen and lung of 1 but the liver, spleen and lungs of the other were free of demonstrable lesions. In 2 of the 3 animals that had negative reactions the parenchymal lesions were limited to non-progressive foci in the lungs, while in the third animal parenchymal lesions were not found.

Attempts to Culture Tubercle Bacilli From the Spleen. When Experiments 1 and 2 were terminated, a portion of the spleen of each animal was suspended and used to inoculate culture media suitable for the growth of tubercle bacilli. Of the 14 spleens representing the untreated controls in Experiment 1, tubercle bacilli were cultured from 12; in 2 the results were negative. Of the 13 spleens from the treated animals in Experiment 1, tubercle bacilli were cultured from only 1; in 12 the results were negative. In Experiment 2, of the 10 spleens from the animals that were not treated, positive results were obtained in 9; in 1 the result was negative. Of the 7 spleens cultured from the animals that had been treated, 2 were positive and 5 were negative. When the data from the 2 experiments are summarized it is revealed that from the spleens of 24 untreated animals positive results were obtained in 21 instances, whereas from the spleens of 20 animals that had received 4,4′-diaminodiphenylsulfone, tubercle bacilli were obtained from only 3; the results in 17 were negative.

Toxicity. As mentioned previously, 4,4′-diaminodiphenylsulfone has been considered a compound of relatively high toxicity. Our data, although not comprehensive, indicate that guinea pigs weighing 1 pound (0.5 kg.) or more will tolerate at least 150 mg. of the drug daily over a long period when the drug is given in the feed. As with the derivatives of 4,4′-diaminodiphenylsulfone, the parent nucleus does induce certain definite changes in the blood. These changes, while of an adverse character, appear in the guinea pig in the dose we have used not to be critical so far as the life of the animal is concerned. The changes are reversible and when the administration of the drug is discontinued the blood is restored to a normal state within a relatively short time. Furthermore, in the dose used, the animals ate well and maintained a presumably normal rate of growth and weight.

Changes of the Blood. Although no attempt was made to obtain detailed information concerning the effect on the blood of 4,4′-diaminodiphenylsulfone in the 3 experiments described, some data were secured

through the kindness of our colleague, Dr. George M. Higgins. At the termination of Experiment 3 (228 days after infection) blood was obtained by cardiac puncture from the 8 surviving animals in the control group and from 6 of the animals that had been receiving 4,4′-diaminodiphenylsulfone for 186 days. The results of the study of the blood are summarized in Table 2.

TABLE 2.—EFFECTS OF 4,4′-DIAMINODIPHENYLSULFONE ON THE BLOOD OF TUBERCULOUS GUINEA PIGS

(The treated animals had received the drug daily in the feed for 186 days)

	Animals	Erythrocytes (millions per c.mm.)	Volume of erythrocytes (cu. μ)	Hemoglobin (gm. per 100 cc. of blood)	Reticulocytes (% of erythrocytes)
Control	8	5.35 ± 0.05*	84.9 ± 0.90	13.3 ± 0.15	1.3 ± 0.17
4,4′-diaminodiphenylsulfone	6	3.63 ± 0.14	123.1 ± 2.30	11.2 ± 0.50	10.3 ± 0.80

* Probable error of the mean.

From the data assembled, it appears that definite destruction of the erythrocytes was exerted by the drug. A hypochromic macrocytic type of anemia was induced. The total number of erythrocytes per c.mm. of blood from the treated animals was 1,720,000 ± 150,000 less than the controls, and the average size of the erythrocytes from the treated animals was 38.2 ± 2.5 cu. μ greater than the controls. This degree of macrocytosis indicates rapid regeneration by the hemopoietic centers. The concentration of hemoglobin per 100 cc. of blood in animals given the drug was 2.1 ± 0.5 gm. less than the controls, a difference which is statistically significant. The high percentage of reticulocytes (10.3 ± 0.8) is further evidence that the hemopoietic centers were not impaired by the drug, which apparently acts directly on the erythrocytes in the circulation.

The concentrations of hemoglobin and of 4,4′-diaminodiphenylsulfone in the blood of the animals in Experiments 1 and 2 are shown in Table 3.

TABLE 3.—CONCENTRATIONS OF HEMOGLOBIN AND OF 4,4′-DIAMINODIPHENYLSULFONE IN THE BLOOD OF GUINEA PIGS THAT HAD RECEIVED THE DRUG FOR 60 DAYS

Experiment	Group	Animals	Average grams of hemoglobin per 100 cc. blood	Average concentration of 4,4′-diaminodiphenylsulfone per 100 cc. of blood
1	Control	14	13.2 (11.2 –15.5)*	
	Treated	13	11.3 (9.1 –12.8)	1.94 (1.41–3.45)
2	Control	10	13.3 (11.2 –15.7)	
	Treated	7	10.1 (1.9†–12.4)	4.1 (1.88–5.76)

* Figures in parentheses represent ranges.

† The guinea pig with the hemoglobin value of 1.9 gm. had, when killed, severe hemorrhagic colitis and a few petechial hemorrhages in the mucosa of the stomach. The lesions mentioned could have accounted for the low hemoglobin value, as a result of hemorrhage.

Comment. These studies, while not exhaustive, do provide sufficient data to establish the fact that 4,4′-diaminodiphenylsulfone under the conditions imposed has a relatively high tuberculotherapeutic efficacy. Not only was the drug capable of exerting a marked deterrent effect on the development of tuberculosis in guinea pigs when the administration of the drug was begun 2 days before the animals were infected, but of much greater importance was the favorable effect achieved when the beginning of treatment was delayed until 6 weeks after the animals

had been inoculated. Conservatively, one must consider the data obtained from the first 2 experiments, which were terminated 60 days after infection, as suggestive rather than convincing evidence of the favorable effect of the drug. The results of the 3rd experiment, which continued for 228 days, were entirely consistent with the situation that appeared so impressive in the experiments of shorter duration. In other words, even though the infective dose of tubercle used in Experiments 1 and 2 was 200 times as great as that used in Experiment 3 and the period of treatment was only 60 days compared with 186 days in Experiment 3, a definite and anatomically significant effect of the drug was demonstrable. In the experiment of longer duration the same favorable anatomic picture was present and the therapeutic effects were more apparent. Fewer lesions were found, and those observed showed a more complete arrest of the disease than occurred in the animals that received the drug for 60 days only.

Whether or not treatment for a period longer than 186 days would have reduced the residual evidence of tuberculous infection still further is problematic, but it would appear to be a reasonable presumption that the retrograde processes evident when Experiment 3 was terminated would have proceeded if the administration of the drug had been continued for an indefinite period.

The data, while suggestive that the drug had exerted a deleterious influence on the tubercle bacilli, are hardly sufficient to justify the conclusion that no viable tubercle bacilli remained in the tissues even in instances in which no lesions were found and in which splenic cultures were negative. To determine this point with certainty, it would be necessary to continue the experiment indefinitely after the period of treatment so as to permit the unhampered development of possible latent infections. However, the facts do indicate that 4,4′-diaminodiphenylsulfone, like several of its derivatives, is capable, in the highly susceptible guinea pig, of coping successfully with a progressive tuberculous process already well established when treatment is started. Even if one assumes that not all the tubercle bacilli are rendered nonviable or destroyed, the treated animal in most instances is able, as a consequence of the drug, to bring to bear on the infective process an enhanced mechanism of resistance that succeeds at least in arresting the disease. This is obviously a highly desirable effect.

The ideal tuberculotherapeutic drug should destroy or inactivate all tubercle bacilli, but it is doubtful if such a goal need be attained. While such a result might be necessary actually to "cure" the disease in the guinea pig, it is generally agreed that this is not necessary in human tuberculosis. Even such successful therapeutic measures as collapse therapy merely render aid to the natural defenses of the human host, without directly or necessarily contributing to the extermination of the tubercle bacilli. It does not seem logical that one should insist that a drug possess powerful bactericidal properties before one considers it for human administration, if bacteriostatic properties would suffice to attain the objectives of treatment.*

* Some pertinent considerations of clinical tuberculochemotherapy have been discussed previously.[6]

Summary and Conclusions. To determine the effect of 4,4′-diaminodiphenylsulfone on the expected course of experimental tuberculosis in guinea pigs, 3 experiments were done. In 2 of the experiments the administration of the drug was started 2 days before the infective agent was introduced and the experiments terminated 60 days after infection. In the 3rd experiment the animals were inoculated with tubercle bacilli 6 weeks before treatment was started. The 3rd experiment was terminated 228 days after infection. All animals were inoculated with the virulent variant of H37 (H37RV). The daily dose of the drug was approximately 150 mg. incorporated with the feed. In the dose employed, the drug exerted only a moderate toxic effect on the blood. Favorable effects of the drug on the infection were definitely apparent in the 2 experiments that were terminated 60 days after infection. These effects were more complete and convincing in the experiment that continued for 228 days than in the short-term experiments. In the long-term experiment, although 71.4% of the untreated animals had died, in the treated group only 28.6% of the animals had died at the conclusion of the experiment. Great differences occurred also in the character and amount of tuberculosis in the treated and untreated groups of animals, those that received the drug either being without demonstrable lesions or having residual foci in which the process was arrested, calcified or healed.

Under the conditions of the experiments, the results indicate (1) that 4,4′-diaminodiphenylsulfone is an effective agent in inhibiting or in combating experimental tuberculosis of guinea pigs; (2) that continuous prolonged administration yields cumulative benefits not attained in short-term experiments; (3) that the drug is not excessively toxic for guinea pigs in the dose used; and (4) that efforts to modify 4,4′-diaminodiphenylsulfone to obtain a compound more suitable for clinical application should be encouraged, since the possibilities seem many.

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EXPERIMENTAL HUMAN INFLUENZA*

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THE experimental production of influenza in human volunteers has great value in testing methods of prevention and treatment which show promise in the laboratory. Relatively small groups of healthy volunteers, well controlled, offer unusual opportunities for the evaluation of new prophylactic and therapeutic methods. Smorodintseff[20] *et al.* inoculated 72 volunteers by inhalation with a 10% suspension of mouse lungs infected with the Leningrad or the W.S. strain of virus. Each volunteer inhaled a calculated 10^5 to 10^6 minimum lethal mouse doses of virus during exposures of from 15 to 60 minutes. Twenty per cent of inoculated individuals showed symptoms diagnostic of influenza. A definite correlation was found between the initial protective titer of the blood and susceptibility to experimental infection, all cases showing clinical symptoms having low initial titers. Increases in neutralizing titers after exposure were noted in most of the volunteers, especially in those showing clinical symptoms following the inhalations.

Burnet and Lush[4] inoculated approximately 150 individuals by intranasal spraying of an egg passage strain of Melbourne virus avirulent for ferrets and mice. No symptoms were observed in exposed subjects and little or no antibody production was demonstrable in a sample group tested.

Chalkina,[6] in experiments on the immunization of volunteers by inhalation of active virus, sprayed a total of 272 men with varying concentrations and doses of mouse lung virus. Definite antibody responses were observed following such exposure and, by controlling the quantity of virus inhaled, undesirable symptoms could be prevented. Of a group subjected to the highest concentration for 30 to 45 minutes, 20% developed symptoms diagnostic of influenza.

Burnet and Foley[5] subjected 15 individuals to repeated insufflations of several viruses, beginning with an avirulent egg-adapted Melbourne strain and concluding with a recently isolated virus. Three of the subjects, all of whom had low initial titers, developed definite symptoms of influenza. The authors emphasize the correlation between low initial antibody level and susceptibility to experimental infection.

Francis[7] inoculated 11 human subjects by intranasal instillation with approximately 500 minimum lethal mouse doses of virus. Only

* The opinions advanced in this publication are those of the writers and do not represent the official views of the Navy Department.

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1 of the subjects showed a definite antibody rise subsequent to the inoculation while none exhibited significant symptoms of influenza.

Henle, Henle and Stokes,[10] employing a strain of virus (F-99) recently isolated from a fatal case, were able to produce influenzal symptoms with temperatures over 100° F. in 10 out of 28 control subjects, and in 1 out of 27 vaccinated subjects. Serologic tests confirmed the observation of Burnet and Foley on the relationship between initial antibody titer and susceptibility to the experimental infection. It was pointed out that individuals with high initial titers subjected to inhalation of the virus did not respond with a significant increase in antibody as did many of the high titer subjects who were vaccinated intramuscularly.

It was our original intention to study the efficacy of immune serum administered by inhalation in the prophylaxis and treatment of experimental human influenza. The whole-hearted coöperation of the officials and several hundred inmates of a California state penal institution was obtained and the preliminary work on optimum infectious dose begun. The project was terminated in this early stage (March, 1943) on orders from the Navy Department, Bur. of Med. and Surg. However, the preliminary data obtained were considered to be of some interest and it is the purpose of this paper to present the methods used and results obtained.

Methods. *Examination of Volunteers.* All volunteers for the experiment were healthy adult males who were subjected to a thorough allergy history questionnaire, skin and conjunctival tests to determine sensitivity to normal horse serum, and a physical examination of the nose, throat, and chest. The questionnaire and allergy tests were conducted in anticipation of the use of the influenzal immune horse serum concentrate. Blood samples were taken by venepuncture at the time of examination, and after clotting the serum was separated by centrifugation, inactivated at 56° C. for 30 minutes, and stored at 4° C. until tested.

Serology. Pre- and postinhalation (2 week interval) serum titers were determined by a red blood cell agglutination inhibition test[15] utilizing human red cells with a constant (1:100) dilution of serum titrated against increasing dilutions of agglutinating virus. Titers are expressed in terms of the fold difference in end-point of agglutination between the test sample and a normal rabbit serum (1:100 dilution) control series. For example, if a test serum has its end-point of agglutination in the tube containing a 1:80 dilution of virus and the normal rabbit serum titer of the virus is 1:2560, the fold difference, or titer, is regarded as 32.

Spraying of the Virus. For the purpose of administering active virus by inhalation we employed glass atomizers of the type described in a separate publication.[16] One of these atomizers was connected at each end of a metal cylinder, 5 feet long and 7 inches in diameter, with 3 openings on each side to which rubber anesthetic masks were attached with flexible rubber tubing (Fig. 1). The outlet valve of the masks allowed escape of some virus fog into the air of the room, but the dilution factor of the air and other precautions taken (see below) minimized the chances of infection of attending personnel. Air at a pressure of 40 cm. Hg was supplied to the atomizers from an electrically driven air compressor. Equilibrium conditions for virus concentration within the chamber were obtained by preliminary atomization for 5 minutes, during which time one outlet functioned through cotton soaked in 5% lysol.

By previous calibration of the atomizers[16] as to air and fluid delivery it was possible to compute the concentration of virus in the air inspired by the

men. Upon completion of the preliminary period of atomization, the air pressure was discontinued momentarily and the connecting tubes immediately attached to the masks on the test subjects. The pressure was again raised to 40 cm. Hg and held until the period of exposure was completed. After removal of the masks the subjects were then hospitalized for at least 5 days either in a small isolated ward room containing 6 beds or in individual isolated cubicles containing 1 bed. The 1 door to the ward was protected by a curtain of ultraviolet light and the room was maintained in a constant atmosphere of propylene glycol dispensed by immersion of an electric light bulb in the solution.[17] The concentration was held at approximately 0.1 mg. propylene glycol per 1000 cc. of air. Similar precautions were taken in the corridor adjacent to the individual rooms housing test subjects and in the room in which the virus spraying was conducted. The insides of the masks were swabbed with 70% alcohol between test groups.

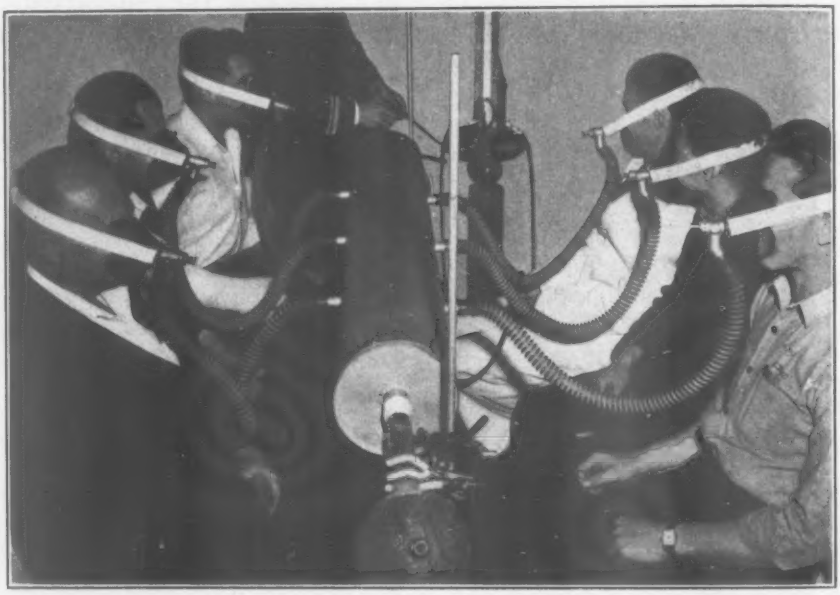

FIG. 1.—Method of administration of influenza virus to volunteers.

Experimental. The preliminary publication by Stokes and Henle[21] on the successful mild infection of humans with a recently isolated "A" type strain of influenza virus (F-99) suggested the possible use of this same infectious agent for our experimental purposes. Dr. Stokes kindly supplied this laboratory with an F-99 infected mouse lung in glycerin. This virus was passed through 4 series of eggs by allantoic inoculation and the final product obtained gave a 50% mortality end-point of $1 \times 10^{-6.6}$ and a red blood cell agglutination end-point of 1:640. This virus suspension, after testing for bacterial sterility, was stored in sterile lusteroid tubes in the dry-ice chamber until ready for use, at which time it was thawed in warm water until clear and then atomized into the chamber for the period scheduled. It was calculated that if the average subject breathed at the rate of 12 liters per minute, approximately 0.3 cc. of the virus was inhaled per minute.

The proportion exhaled is an unknown, although it has been estimated by Heubner[11] to be between 50 and 80% of the quantity inhaled.

Six groups of 6 men each were successively sprayed with this fluid, the exposure periods being increased on each succeeding group until 1-, 3-, 6- and 12-minute exposures had been attempted. No significant symptoms were observed in any of the 24 test subjects. Blood counts showed no significant changes. Pre- and postinhalation titers against F-99 egg agglutination virus were determined by the red blood cell agglutination inhibition method. Only 4 individuals out of the 24 showed a four-fold or greater antibody titer rise.

During the period of investigation of the infectivity of the F-99 virus, a number of cases of suspected influenza appeared in a Naval training station in this area. Rhinopharyngeal washings were obtained from 5 patients exhibiting symptoms of influenza.[18] In each case 20 to 25 cc. of nutrient broth, pH 7.1, were injected into the rhinopharynx through a rubber catheter. The subject was instructed not to swallow the broth but to eject it through the mouth into an emesis basin. The washings were then transferred to a sterile lusteroid tube and immediately stored in a dry-ice chamber.

Various methods for the isolation of influenza virus from such material have undergone trial in numerous research laboratories since the original isolation of the virus in the ferret by Smith, Andrewes and Laidlaw.[19] While the ferret has proved of great value in the study of influenza epidemics,[14] mice, tissue culture media, and the chorioallantoic membrane of the chick embryo also have been advocated for primary virus isolation.[8,9,10] Taylor and his associates have reported that hamsters compare favorably with ferrets for direct isolation from nasopharyngeal washings.[22,24,25] Burnet[2,3] has successfully applied the amniotic inoculation of chick embryos, pioneered by Buddingh and Polk[1] in their study of meningococcal infections. He claims that unadapted influenzal virus is capable not only of infecting the chick embryo, but of producing easily recognizable effects in the embryo as well. The use of chick embryos for rapid isolation and identification of virus received a great stimulus from the work of Hirst[12,13] on the hemagglutinability of virus-containing allantoic fluid. The application of this phenomenon has measurably reduced the time required for isolation and identification of influenza strains.

The procedure employed on the 5 rhinopharyngeal washings obtained from Naval personnel was as follows: An attempt was first made to break up the clumps of mucous material in the thawed sample by repeatedly filling and emptying the washings through a 30 cc. syringe fitted with a 20 gauge or 23 gauge needle. The sample was then angle-centrifuged at 5000 r.p.m. for 20 minutes and subsequently 0.1 to 0.2 cc. of the supernatant fluid was inoculated into the amniotic sac of each of eight 13-day old embryos, according to the technique described by Taylor and Chialvo.[23] Following 36 to 40 hours incubation at 37° C. blood-free allantoic fluid from each of the live embryos, and a few dead embryos, was collected and a 10% saline suspension of the pooled, ground tracheas was prepared. Alundum and the larger tissue

particles of the tracheal suspension were removed by low-speed centrifugation. The allantoic fluid from each embryo and the tracheal suspension were then tested for the presence of hemagglutinins. If these proved negative, 0.1 to 0.2 cc. of the tracheal fluid was reinoculated into the amniotic sac of each of 8 embryos and the described procedure repeated.

Of the 5 rhinopharyngeal washings tested, 2 showed the presence of virus in the first egg passage, and the remaining 3 were positive by the third egg passage. Inhibition tests of each virus against PR8 and Lee rabbit-immune sera indicated all 5 to be "A" type. There appeared definite variation in the adaptability of the viruses for mice, 2 of the strains requiring but 1 egg passage to become lethal for mice while the remaining 3 required up to 7 passages to attain this degree of virulence.

Attempts to isolate virus from these same washings by means of hamsters, according to the technique of Taylor,[25] or by direct inoculation into mice, proved entirely negative.

One of the viruses appearing in the first egg passage was inoculated into a group of mice, from which 2 further egg passages into the allantoic fluid of 11 day old embryos were made. This final egg passage furnished the virus used for infection of the next series of volunteers. It had an agglutination end-point of 1:1280, which was inhibited by a PR8 immune rabbit serum, but not by a Lee immune serum. The same technique of human inoculation was employed with this virus and 3 exposure periods were tested as follows: 6 men for 6 minutes, 5 men for 10 minutes, and 6 men for 12 minutes. These subjects were likewise hospitalized and blood counts performed on the 1st, 3rd and 5th day in some and every day in others by inmate personnel. Temperature readings were taken at least twice a day.

Of these 17 volunteers, 10 showed signs and symptoms of influenza. Of the 10, 4 were regarded as typical clinical influenza and 6 as highly suggestive of this disease. Table 1 summarizes the occurrence of the various signs and symptoms in these 10 cases.

TABLE 1.—SUMMARY OF OCCURRENCE OF VARIOUS SIGNS AND SYMPTOMS IN 10 VOLUNTEERS SHOWING SIGNS OF INFLUENZA

Symptom	No. of volunteers showing symptom
Fever over 100° F.	7
Feeling of feverishness	10
Malaise	10
Headache	9
Backache	6
Generalized ache	5
Tightness in chest	2

The 3 men who reported feeling feverish, but who are not included in those showing a temperature over 100° F., very likely would have shown a significant temperature had the readings been taken at the proper time. It was believed that the peaks had been missed in these cases, although the transitory nature of the temperature rises indicated only a mild reaction.

The onset of the fever and symptoms occurred 9 to 12 hours following exposure in 3 of the subjects, and between 24 and 30 hours in the remaining 7. No signs of upper respiratory infection were observed in any of the patients, nor were any indications of lung involvement noted. The blood counts showed no significant changes, but there is reason to believe that the blood counts undertaken by inmate personnel were not entirely reliable. Henle, Henle and Stokes[10] noted a significant leukopenia (below 5000) and a relative lymphocytosis in a considerable proportion of their subjects, in those showing no outward signs of infection as well as in the outright cases. It was our intention to follow this aspect of the experiment more closely and perform the counts ourselves had it been possible to continue our experiments. We had the distinct impression that the leukopenia accompanying naturally occurring influenza was an inconstant finding and of doubtful value in diagnosis.[16]

A summary report of 1 of the 4 definite cases resulting from the inhalation of the virus follows:

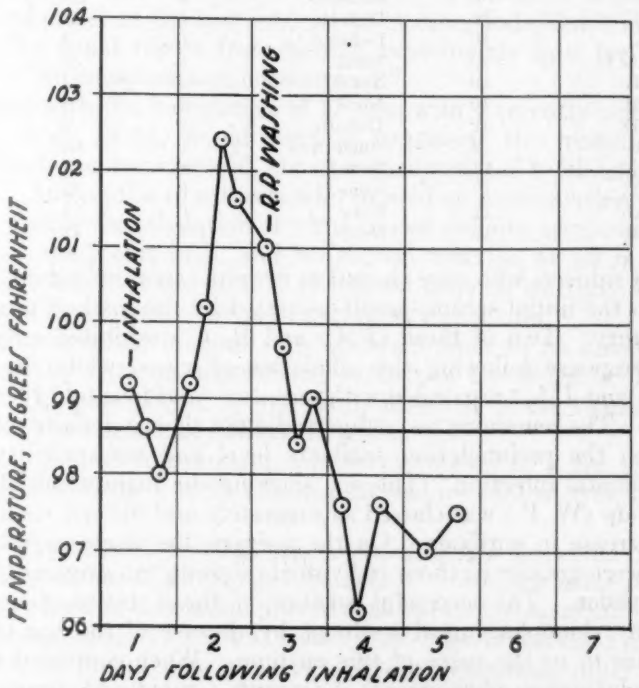

FIG. 2.—Temperature chart on "R. C." exposed to influenza virus 6 minutes.

Case Studies. "R. C."—preliminary physical exmination was negative. Subject was exposed 3/9/43 to a spray of TI 2A influenza virus for 10 minutes and then hospitalized. About 9 hours after the inhalation period he felt feverish and developed general malaise. This was followed shortly by headache, backache, aching legs, and a sense of "tightness and burning" in the chest. The temperature rose to 102.4° F. and remained elevated about 36 hours. Upon physical examination the facies appeared flushed and dry with mild con-

junctival injection. The lungs were clear. The spine was moderately stiff. The aches and pains, malaise and headache persisted for 48 hours and were followed by general weakness for 48 hours. Daily blood counts showed no significant changes. The temperature chart on this case is presented in Figure 2.

Approximately 48 hours after inhalation of the virus, rhinopharyngeal washings were obtained from this subject and the technique for the isolation of virus followed as described. By the 6th egg passage a positive agglutinating virus appeared which was inhibited by a PR8 immune rabbit serum while unaffected by a Lee immune serum.

Results of the agglutination inhibition tests on all 17 men against the specific TI virus are presented in Table 2.

TABLE 2.—RESULTS OF AGGLUTINATION INHIBITION TESTS

Subject	Time of exposure (min.)	Symptoms	Preinhalation titer	Postinhalation titer	Fold rise in titer
E. S.	6	Suggestive	4	8	2
E. F.	6	Suggestive	0	8	8
W. S.	6	Suggestive	0	8	8
N. W.	6	Suggestive	4	8	2
W. F.	6	Suggestive	16	16	0
J. C.	6	Definite	0	128	128
R. C.	10	Definite	0	32	32
J. L.	10	Definite	0	4	4
E. A. G.	10	None	8	32	4
C. E.	10	None	8	64	8
E. H.	10	None	2	8	4
R. D.	12	Definite	0	2	2
F. G.	12	Suggestive	0	64	64
N. M.	12	None	0	8	8
L. T.	12	None	0	32	32
E. G.	12	None	0	4	4
G. B.	12	None	8	32	4

All 4 subjects who were classed as definite cases showed no antibody titer in the initial serum sample as tested by the method used in this laboratory. Two of these (J. C. and R. C.) exhibited strong antibody response following the inhalation of virus, while the other 2 (R. D. and J. L.) responded with only two- and four-fold rises respectively. The remaining test subjects did not show a definite correlation between the preinhalation antibody level and susceptibility to the experimental infection. The one showing the highest initial titer in the group (W. F.) was classed as suggestive and did not respond with any increase in antibody. On the average, the increases in antibody titers were greater in those individuals showing no original titer.

Discussion. The successful isolation of the 5 strains of virus from as many rhinopharyngeal washings by the use of the egg technique indicates to us the value of this medium. When combined with the hemagglutination phenomenon it presents a rapid and simple method of virus identification. In some cases bacterial contaminants will present difficulties necessitating the use of a filter, which no doubt removes considerable virus as well as bacteria, but at present no other certain method is available. Hirst[13] has recently discussed these points.

The failure to produce clinically recognizable infection with the F-99 strain of virus, even with doses several times that employed by Henle,

Henle and Stokes, may possibly be due to the extra egg passages through which this virus was carried before inoculation of our test subjects. The mouse lethal titer of the suspension used compared favorably with the titer reported in their successful experiment, but, of course, such measurements are no guarantee of infectiousness for humans. It is not easily understandable, however, why a virus infective for man after having been passed 16 times in experimental animals and 3 times in eggs should, after but 4 more egg passages, be so innocuous. It may be that virulence alterations of influenza viruses take place in sudden steps rather than by gradual decline. If such is actually the case, a few passages from human to human under proper conditions might bring about the reverse transition, thereby fulfilling the primary requirement for development of a severe epidemic. The possibility of such an occurrence makes one hesitate before advocating immunization of humans by means of attenuated virus administered by inhalation.

Clinical experiments on infection of human volunteers with influenza virus, when precautions of isolation are taken, do not seem to constitute a hazard either to the test subjects or to other individuals in the vicinity. The usual report from human experiments thus far performed is: "No complications encountered."

Our results with the inoculation of 17 men with a recently isolated "A" type virus, TI 2A, would seem to emphasize the tremendous individual variation encountered, not necessarily related to blood antibody level. Among the 10 subjects who showed no preinhalation titer in our test group, the inhalation of virus caused definite symptoms in 4, suggestive symptoms in 3, and no clinical reaction at all in the remaining 3. Only 1 of the total of 17 did not respond with any antibody rise and, significantly, he had the highest initial titer.

Questions concerning immunity to influenza seem to be answered only partially by data on neutralizing content of the blood or nasal secretions. The part played by the tissue involved in the virus-host reaction is as yet vague and difficult to assess.

Summary. Twenty-four human volunteers exposed to a fine spray of F-99 egg virus from 1 to 12 minutes showed no clinical symptoms of influenza.

Five "A" type strains of virus were isolated from 5 suspected cases of influenza by means of direct egg inoculation. Methods using hamsters and mice for direct isolation proved negative on the same samples.

One of these strains, TI 2A, was used for infection of a second series of volunteers in preliminary work on optimum infectious dose. Of 17 subjects exposed from 6 to 12 minutes, 4 exhibited definite symptoms of influenza, 6 were highly suggestive, while the remainder showed no significant reactions. The blood counts, as reported to us, revealed no changes. No complications were encountered.

The 4 definite cases all had low initial antibody titers. All but 1 of the 17 test subjects showed some antibody rise as a result of the inhalation. The exception had the highest initial antibody titer of the group.

An "A" type virus was isolated from one of the definite cases. No other attempts at isolation were made in this group.

We acknowledge with pleasure the helpful coöperation of Mr. Clinton T. Duffy, Warden of San Quentin Prison, Dr. Alex Miller, Chief Surgeon, and the members of the California State Prison Board. We also wish to express appreciation for the technical assistance rendered by Mr. James W. Ford.

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A NOTE RECOMMENDING THE USE OF DRIED PLASMA OBTAINED FROM FRESH CADAVER BLOOD*

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Because of the urgent and immediate wartime need of large amounts of plasma, it was suggested in a previous paper,[1] and indirectly in another,[4] that cadaver blood be processed into dried plasma or, preferably, into dried albumin (since albumin is the effective anti-shock

* As the chief objection to the use of suitably collected postmortem blood seems to be one of sentiment, we are glad to publish this note recommending the procedure. Especially today, when so much effort and expenditure of valuable working hours are being put into Blood Donation, it would seem that this method, granted of course that the product was sterile and innocuous, might well prove to be a desirable auxiliary or substitute.—Editor.

fraction and is precipitated from plasma by the aid of alcohol-water mixtures), because it is available in large quantities at the undertaking establishments of the United States and, of course, can be obtained without initial expense.[2] Unfortunately, the use of cadaver blood is looked upon with some disrepute in this country;[1] there is "something revolting to Anglo-Saxon susceptibilities in the proposal of using cadaver blood,"[3] but this feeling has been overcome in other countries such as Russia.[5–8] It can be pointed out that no one objects to receiving products of dead animals, such as liver extract, insulin, gelatin, isinglass (fish bladders), hormones, enzymes, and so forth, or to the transplantation of corneæ, nerves and, I am told, even of skin of cadavers; and that the blood of cadavers can, if transfused, "live on" and, therefore, would not be subjected to decomposition with the cadaver. In spite of the existence of this stigma, permission was obtained from the hospital authorities to administer the plasma of a recently deceased cadaver to a patient with a malignant disease. The dried plasma was restored to one-fourth its original fluid volume, injected, and the changes observed. Such a procedure apparently has not been recorded before.

Technique. Through the coöperation of Oliver H. Bair Company, a Philadelphia undertaker a cadaver was obtained. The individual had died suddenly of "heart disease" some 8 hours previous to the withdrawal of blood. The usual undertakers' type of artery and vein cannulæ were thoroughly washed, sterilized and aseptically inserted into the brachial artery and vein, as requested by the undertakers. (Yudin[7] has shown that the easiest way to obtain blood from a cadaver is to cut the jugular vein in two and to insert a glass U-shaped cannula into the vein above the cut and a long glass cannula, which reaches to the right auricle, into the vein below the cut. The cadaver is placed in the Trendelenburg position, and the blood flows out by gravity. Blood is collected from the systemic veins thereby and not from the portal system, the blood from which could be contaminated easily with bacteria from the gastro-intestinal tract. Yudin collects from 1.5 to occasionally as much as 4 liters of blood per cadaver by this method. He recommends that the individual be dead no longer than 8 hours.) Five pints of sterile saline was forced into the arterial system with a sterilized rubber bulb pump, and 4 pints of cadaver blood mixed with saline were obtained by the "closed" system. The vein cannula was connected by rubber tubing to a sterile needle which was inserted into transfusion bottles (Hospital Liquids Incorporated) in which a partial vacuum exists. The 4 bottles were centrifuged. The 1st and 3rd bottles containing sodium citrate had total volumes of 510 and 575 cc. and 160 and 70 cc. of packed red blood cells respectively; the 2nd and 4th bottles, which contained no citrate (evidences of clotting were noted 4 to 6 hours after withdrawal), had total volumes of 500 and 600 cc. and 40 and 25 cc. of packed red blood cells respectively. The plasma of the 1st and 3rd bottles was combined, cultured, frozen in glass ampoules, dried by the Adtevac process[1] and recultured after being dried; the serum of the 2nd and 4th bottles was treated likewise: 30.5 gm. of dried plasma and 14 gm. of dried serum were obtained.

The plasma and serum were restored to one-fourth of their original volumes with distilled water[1] and administered intravenously to a patient with a teratoma (but who was in "good" physical health). Both plasma and serum were given after a lapse of more than 10 days to note if antibodies might have developed. The patient finally succumbed on December 1, some 6 or 7 weeks after the last administration of cadaver plasma. The microscopic examination of the organs revealed no changes that might be ascribed to the use of cadaver plasma.

Results. The serologic and cultural studies were negative. As can be observed in Table 1, the dried cadaver plasma and serum seemed to have similar effects as did the dried donor plasma. No reactions, febrile, anaphylactoid, urticarial, hemolytic or antigenic, were noted in the patient.

TABLE 1.—THE BLOOD PRESSURE, HEMATOCRIT AND PLASMA PROTEIN LEVELS BEFORE AND AFTER THE INTRAVENOUS ADMINISTRATION OF 4 TIMES CONCENTRATED PLASMA OF BOTH DONOR AND CADAVER ORIGIN TO A PATIENT OVER A 25 DAY PERIOD

Date	Type of plasma or serum	Amount injected (gms. plasma in c.c. aq. dist.)	Blood pressure	Hematocrit	Plasma protein (falling drop method)
9–17–43	Donor plasma	8 gm. in 40 cc.	124/68	33	6.53
	15 minutes after administration		132/80	31	6.19
9–18–43	*Cadaver plasma*	8 gm. in 40 cc.	122/82	32	6.6
	15 minutes after administration		132/85	31	6.9?
9–20–43	Cadaver serum	8 gm. in 40 cc.	120/68	34	6.6
	15 minutes after administration		110/75	30	6.2
9–29–43	*Cadaver plasma*	8 gm. in 40 cc.	102/64	32	7.2
	15 minutes after administration		115/70	32	7.0
10– 6–43	Cadaver serum	1 gm. in 4 cc.	..	..	..
10–12–43	*Cadaver plasma*	8 gm. in 40 cc.	120/65	31	7.1
	15 minutes after administration		124/70	29	6.7

Conclusions. The collection, preparation and administration of dried plasma from cadaver blood is a practical procedure and is recommended during our present wartime emergency. After the war, the commercial houses could probably supply the nation's albumin or plasma needs from cadaver blood. Recommendations could easily be made for the selection of cadavers (cause of death, time of death, etc.) and for techniques of collecting and appropriately processing (into dried plasma or probably preferably, dried albumin) cadaver blood obtained at mortuaries or hospitals. The use of products of cadaver blood should be reconsidered by the medical profession of the United States and Great Britain.

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ELECTROCARDIOGRAPHIC PATTERNS IN CARDIOVASCULAR SYPHILIS*

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The pathology and pathogenesis of cardiovascular syphilis are more completely understood today than when Lancisii[26] first showed that the aneurysms observed by Paré[31] were the result of the disease.[5,10,22] Apparently the spirochetes establish a bridgehead in the wall of the aorta, invade the aortic wall, and weaken it until dilatation or aneurysm results. There also may be a downward infiltration involving the aortic valve, causing ring dilatation and valvular deformity leading to aortic regurgitation. Because the sinuses of Valsalva are favorite locations for the syphilitic involvement, the mouths of the coronary arteries are often encroached upon and occasionally are completely obliterated by the syphilitic process. Secondary to the coronary ostial involvement, there is often interference with the blood supply of the heart which leads to damage to the myocardium ranging from mild fibrosis to infarction. This, and more particularly the aortic regurgitation, often lead to cardiac hypertrophy.

Previous authors are in accord that the electrocardiogram is unchanged in early cardiovascular syphilis,[1,14,19,38,39] but in the later stages when the coronary ostia and the aortic valves are involved, electrocardiographic abnormalities are encountered. Most of the reports[1,6,12,14,17,19,20,37,39] have consisted of a description of the deviations of the various individual components, especially QRS and T, although instances of A-V[1,12,17,20,37] and intraventricular block[1,6,12,14,20,37] have been noted. When left ventricular preponderance was diagnosed it was commonly done so on the basis of left axis deviation alone,[14,17,27,37] abnormalities of the S-T-T component being attributed to coronary insufficiency.[20] Stressing the significance of S-T-T changes in left heart strain, Barnes and Whitten[4] included 8 examples of left ventricular preponderance due to cardiovascular syphilis in their illustrative cases. Ashman and Hull[2] also noted the presence of S-T-T- changes in left ventricular hypertrophy due to syphilitic aortic regurgitation.

Only a few correlations of electrocardiographic changes with postmortem findings have been reported.[6,12,20,37] It is the purpose of this paper to analyze the electrocardiograms in autopsied cases of cardiovascular syphilis in terms of special patterns which have recently been observed to occur under specific circumstances.[3,23,24] The analysis is based on a series of 30 consecutive necropsied cases. Such a

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† This is an abridgment of a thesis submitted by Dr. Cole to the Faculty of the Graduate School of Medicine of the University of Pennsylvania toward the requirements for the degree of Master of Medical Science (M.Sc.[Med.]) for graduate work in internal medicine.

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TABLE 1.—CASES IN WHICH SYPHILIS WAS THE SOLE FACTOR LEADING TO CARDIAC ABNORMALITIES RESPONSIBLE FOR ELECTROCARDIOGRAPHIC CHANGES

Case	Anatomic changes: Syphilitic	Anatomic changes: Associated	Heart weight (gm.)	Ventricular thickness (mm.): Left	Ventricular thickness (mm.): Right	Electrocardiographic patterns	Age (yrs.)	Blood pressure (mm. Hg)	Illustrated in Figures—
1	1. Multiple aneurysms of arch of aorta 2. Aortitis 3. Aortic regurgitation	.....	350	19	8	Left ventricular preponderance, 2nd type	68	135/85	1 *A*
2	1. Aortitis 2. Aortic regurgitation 3. Both coronary ostia markedly stenosed	1. Healed mitral and aortic endocarditis	450	20	6	Left ventricular preponderance, mixed type	55	150/100	1 *B*
3	1. Aortitis 2. Aortic regurgitation 3. Both coronary ostia encroached upon	1. Myocardial fibrosis	435	25	6	Left ventricular preponderance, mixed type	53	150/40	1 *C*
4	1. Aortitis 2. Aneurysm of innominate artery 3. Aortic regurgitation 4. Right coronary ostium encroached upon	1. Mild coronary sclerosis; all lumens patent	730	18	5	Left ventricular preponderance, mixed type	64	170/40	1 *D*
5	1. Aortitis 2. Aortic regurgitation 3. Right coronary ostium completely obliterated; left narrowed	1. Myocardial fibrosis	550	14	3	Left ventricular preponderance, 2nd type; progressing to intraventricular block of 1st indeterminate type	47	180/56	1 *H*
6	1. Aortitis 2. Aortic regurgitation 3. Both coronary ostia markedly narrowed	1. Slight coronary sclerosis; all lumens patent 2. Myocardial fibrosis 3. Infarction of anterior wall of left ventricle	400	24	3	Pattern associated with infarction of anterior wall of left ventricle; Lead 1, atypical	63	110/50	1 *E*
7	1. Aortitis 2. Aneurysm of ascending aorta 3. Marked narrowing of left coronary ostium 4. Aortic regurgitation	1. Slight coronary sclerosis; all lumens patent 2. Infarction of apex of left ventricle	575	17	2	Pattern associated with infarction of anterior wall of left ventricle (QRS 2 and 3 down and larger than upright QRS 1)	56	146/42	1 *F*
8	1. Aortitis 2. Aneurysm of sinus of Valsalva and arch of aorta 3. Aortic regurgitation 4. Right coronary ostium completely obliterated; left narrowed	1. Slight coronary sclerosis; all lumens patent 2. Early infarction of septum	580	17	2	Intraventricular block of indeterminate S type; A-V block	44	160/50	1 *G*

TABLE 2.—CASES IN WHICH THE SYPHILITIC ANATOMIC ABNORMALITIES WERE COMBINED WITH THOSE OF OTHER ETIOLOGIC FACTORS TO PRODUCE THE ELECTROCARDIOGRAPHIC PICTURE

Case	Anatomic changes: Syphilitic	Anatomic changes: Associated	Heart weight (gm.)	Ventricular thickness (mm.): Left	Ventricular thickness (mm.): Right	Electrocardiographic patterns	Age (yrs.)	Blood pressure (mm. Hg)	Illustrated in Figures—
9	1. Aortitis 2. Aneurysm of ascending aorta 3. Aortic regurgitation 4. Both coronary ostia markedly encroached upon	1. Myocardial fibrosis 2. Old pyelonephritis and arteriosclerotic changes of kidneys	700	20	8	Left ventricular preponderance, concordant type	65	210/48	2 *A*
10	1. Aortitis 2. Aortic regurgitation 3. Moderate stenosis of both coronary ostia	1. Coronary sclerosis with narrowing of lumens 2. Old healed posterior wall infarction 3. Myocardial fibrosis 4. Acute verrucous superimposed on an old fibroplastic mitral and aortic endocarditis	650	15	4	Left ventricular preponderance, 2nd type	47	176/66	2 *B*
11	1. Aortitis 2. Aneurysm of ascending aorta 3. Aortic regurgitation 4. Narrowed rt. coronary ostium	1. Slight coronary sclerosis; all lumens patent 2. Myocardial fibrosis 3. Nephrosclerosis of arteriolar variety	710	21	4	Left ventricular preponderance, 2nd type; auricular fibrillation	66	250/110	2 *C*
12	1. Aortitis 2. Aortic regurgitation	1. Slight coronary sclerosis; all lumens patent 2. Arteriosclerotic changes of aortic valve 3. Myocardial fibrosis 4. Acute interstitial nephritis and early nephrosclerosis of arteriolar variety 5. Acute vegetative endocarditis of mitral and tricuspid valves	675	16	2	Left ventricular preponderance, 2nd type; frequent auricular premature contractions	55	184/74	2 *D*
13	1. Aortitis 2. Aneurysm of ascending aorta 3. Aortic regurgitation	1. Myocardial fibrosis 2. Subacute glomerulonephritis	775	18	5	Left ventricular preponderance, mixed type	34	224/118	2 *E*
14	1. Aortitis 2. Aortic regurgitation	1. Marked coronary sclerosis with narrowing of the lumens, the right especially 2. Arteriosclerosis of aortic valve 3. Nephrosclerosis of arteriolar type	550	10	4	Left ventricular preponderance, 2nd type	62	226/122	2 *F*
15	1. Aortitis 2. Marked narrowing of right coronary ostium	1. Old occlusion of left coronary artery 2. Old apical and septal infarction 3. Myocardial fibrosis 4. Nephrosclerosis of arteriolar type	425	10	..	Intraventricular block of indeterminate S type; deep Q in CF_2 is suggestive of old anterior wall infarction	60	170/110	2 *G*

TABLE 2.—(*Continued*)

Case	Anatomic changes: Syphilitic	Anatomic changes: Associated	Heart weight (gm.)	Ventricular thickness (mm.): Left	Ventricular thickness (mm.): Right	Electrocardiographic patterns	Age (yrs.)	Blood pressure (mm. Hg)	Illustrated in Figures—
16	1. Aortitis 2. Aneurysm of ascending aorta 3. Aortic regurgitation	1. Moderate coronary sclerosis with narrowing of lumens 2. Myocardial fibrosis 3. Nephrosclerosis of arteriolar type	475	14	5	Intraventricular block of common type	50	154/90	2 *H*
17	1. Aortitis 2. Aneurysm of sinus of Valsalva 3. Narrowing of right coronary ostium 4. Aortic regurgitation	1. Marked coronary sclerosis with narrowing of lumens, left especially 2. Old healed lateral wall infarction 3. Septal scar	600	15	6	Anterior wall pattern of myocardial infarction with septal involvement suggested by partial A-V block	57	144/44	2 *I*
18	1. Aortitis 2. Aortic regurgitation 3. Marked narrowing of both coronary orifices	1. Mild coronary sclerosis; all lumens patent 2. Myocardial fibrosis 3. Mitral endocarditis and stenosis 4. Congenital bicuspid aortic valve 5. Nephrosclerosis of arteriolar type	550	21	5	Non-specific abnormalities including T-wave changes in chest lead during an attack of pain	60	146/60	2 *K*
19	1. Aortitis 2. Aneurysm of ascending and descending aorta 3. Marked narrowing of right coronary ostium	1. Moderate sclerosis of both coronary arteries with narrowing of lumens 2. Myocardial fibrosis 3. Emphysema 4. Miliary tuberculosis including myocardium	350	12	1	Non-specific abnormalities including low voltage	59	128/80	2 *J*

TABLE 3.—CASES IN WHICH SYPHILIS WAS MERELY COINCIDENTAL AND THE ELECTROCARDIOGRAPHIC FINDINGS WERE ASCRIBED TO OTHER NON-SYPHILITIC ETIOLOGIC FACTORS

20	1. Aortitis	1. Moderated coronary sclerosis, lumens narrowed 2. Nephrosclerosis of arteriolar type	575	13	7	Left ventricular preponderance, concordant type	59	174/120	3 *A*
21	1. Aortitis 2. Multiple aneurysms of aorta	1. Marked sclerosis of both coronary arteries with narrowing of lumens 2. Nephrosclerosis of arteriolar type 3. Myocardial fibrosis	425	13	3	Left ventricular preponderance, 2nd type	64	170/90	3 *J*
22	1. Aortitis	1. Mild coronary sclerosis, lumens patent 2. Nephrosclerosis of arteriolar type	675	20	6	Left ventricular preponderance, concordant type	69	190/100	3 *C*
23	1. Aortitis 2. Aneurysms of ascending aorta	1. Marked coronary sclerosis of both coronary arteries and occlusion of right circumflex	600	15	6	Right ventricular preponderance, "mitral" P waves. Note: electrocardiogram was taken before episode of recent infarction.	44	150/110	3 *D*

22	1. Aortitis	1. Mild coronary sclerosis, lumens patent 2. Nephrosclerosis of arteriolar type	375	20	6	Left ventricular preponderance, concordant type	69	190/100	3 *C*
23	1. Aortitis 2. Aneurysms of ascending aorta	1. Marked coronary sclerosis of both coronary arteries and occlusion of right circumflex 2. Old healed infarct of lateral wall and recent infarct of septum and anterior wall of left ventricle 3. Mitral endocarditis	600	15	6	Right ventricular preponderance, "mitral" P waves. Note: electrocardiogram was taken before episode of recent infarction.	44	150/110	3 *D*
24	1. Aortitis	1. Moderate sclerosis of both coronary arteries with narrowing of lumens 2. Bronchiectasis 3. Advanced pulmonary tuberculosis	240	15	1.5	Right axis shift and non-specific abnormalities including many auricular, nodal and ventricular premature contractions	66	92/40	3 *E*
25	1. Aortitis	1. Mitral endocarditis and stenosis 2. Myocardial fibrosis	375	10	4	Right ventricular preponderance; also "mitral" P waves	48	122/90	3 *F*
26	1. Aortitis 2. Aortic regurgitation	1. Marked coronary sclerosis of both coronary arteries with occlusion of lumens 2. Healed posterior wall infarction 3. Nephrosclerosis of arteriolar type 4. Healed mitral and aortic endocarditis 5. Bicuspid aortic valve (congenital)	500	15	3	At first left ventricular preponderance, 2nd type; then, persistent posterior wall pattern associated with myocardial infarction, and intraventricular block	59	150/74	3 *K*
27	1. Aortitis	1. Marked coronary sclerosis with narrowing of lumens (both arteries) 2. Infarct of the lateral wall of left ventricle	350	16	3	Non-specific abnormalities including S-T depressions in all limb leads. Note: electrocardiogram was taken before infarction episode	60	155/100	3 *G*
28	1. Early aortitis	1. Stab wound involving pericardium and myocardium of right ventricle 2. Acute fibrinous pericarditis 3. Hemopericardium	300	..	..	Findings resemble those seen in acute diffuse pericarditis	33	100/60	3 *H*
29	1. Aortitis 2. Aortic regurgitation 3. Narrowing of both coronary ostia	1. Acute myocarditis 2. Subacute vegetative endocarditis involving the aortic and mitral valves; old rheumatic valvulitis 3. Acute and chronic glomerulonephritis 4. Congenital bicuspid aortic valve	425	20	6	Within normal limits	51	150/60	3 *I*
30*	1. Aortitis 2. Aneurysms of the ascending arch and descending aorta 3. Aortic regurgitation 4. Narrowing of both coronary ostia	1. Mild coronary sclerosis; all lumens patent 2. Myocardial fibrosis	270	10	2	Non-specific abnormalities including low voltage of limb leads	51	165/90	3 *B*

* Vitamin B deficiency.

study might establish any electrocardiographic patterns or changes peculiar to syphilis and would delineate the respective rôle played by the individual syphilitic lesion as well as that of any other associated etiologic factor present. For this purpose, the cases were subdivided into 3 categories: (1) Cases in which syphilis was the sole factor leading to cardiac abnormalities responsible for the electrocardiographic changes (Table 1). (2) Cases in which the syphilitic anatomic abnormalities were combined with those of other etiologic factors to produce electrocardiographic changes (Table 2). (3) Cases in which syphilis was merely coincidental and the electrocardiographic changes were primarily ascribed to other non-syphilitic findings (Table 3).

TABLE 4.—SUMMARY OF ANATOMIC AND ELECTROCARDIOGRAPHIC FINDINGS

	Anatomic changes										Electrocardiographic patterns					
	Cardiac hypertrophy	Aortic regurgitation	Coronary ostial stenosis		Coronary sclerosis		Myocardial infarction	Myocardial fibrosis	Hypertension*	Misc. concomitant factors	Left ventricular preponderance	Right ventricular preponderance	Infarction patterns	Intraventricular block	A-V block	Other non-specific abnormalities
Case No.			R	L	R	L										
1	L/r	x	..	..	..	..	..	..	..	..	x	..	..	..	..	..
2	L/r	x	3+	3+	..	..	..	..	..	..	x	..	..	..	..	..
3	L/r	x	1+	1+	..	..	..	x	..	..	x	..	..	..	..	..
4	L/r	x	2+	..	..	..	..	..	..	..	x	..	..	..	..	..
5	L	x	4+	3+	..	..	..	x	..	..	x	..	..	x	..	..
6	L	x	3+	3+	..	..	x	x	..	..	..	..	A	..	..	..
7	L	x	..	3+	..	..	x	..	..	..	..	..	A	..	..	..
8	L	x	4+	3+	..	..	x	..	..	..	..	..	..	x	x	..
9	L/r	x	3+	3+	..	..	..	x	x	..	x	..	..	..	..	..
10	L/r	x	2+	2+	1+	1+	x	x	..	..	x	..	..	..	..	..
11	L/r	x	1+	..	..	..	..	x	x	..	x	..	..	..	..	..
12	L	x	..	..	..	..	..	x	x	..	x	..	..	..	..	x
13	L/r	x	..	..	..	..	..	x	x	..	x	..	..	..	..	x
14	L/r	x	..	..	2+	1+	..	..	x	..	x	..	..	..	..	..
15	L	..	3+	..	..	3+	x	x	x	..	..	..	..	x	..	..
16	L/r	x	..	..	1+	1+	..	x	..	..	..	..	..	x	..	..
17	L/r	x	1+	..	1+	2+	x	..	..	..	..	..	A	..	x	..
18	L/r	x	3+	3+	..	..	..	x	..	x	..	..	..	..	..	x
19	L/r	..	3+	..	1+	1+	..	x	..	x	..	..	..	..	..	x
20	L.R.	..	..	..	1+	1+	..	..	x	..	x	..	..	..	..	..
21	L	..	..	..	2+	2+	..	x	x	..	x	..	..	..	..	..
22	L/r	..	..	..	..	..	..	..	x	..	x	..	..	..	..	..
23	L.R.	..	..	..	3+	2+	x	..	x	x	..	x	..	..	..	..
24	L	..	..	..	2+	2+	..	..	..	x	..	..	..	..	..	x
25	R	..	..	..	..	..	..	x	..	x	..	x	..	..	..	..
26	L	x	..	..	3+	3+	x	..	..	..	x	..	P	x	..	..
27	L	..	..	..	2+	2+	x	..	..	..	..	..	..	..	..	x
28	..	..	..	..	..	..	..	..	..	x	..	..	†	..	..	..
29	L/r	x	2+	2+	..	..	..	..	..	x	..	..	..	..	..	..
30	..	x	1+	1+	..	..	..	..	..	x	..	..	..	..	..	x

L = Left ventricular hypertrophy. R = Right ventricular hypertrophy. L/r = Predominantly left ventricular hypertrophy. L.R. = Both ventricles hypertrophied, neither predominantly. A = Anterior wall. P = posterior wall.

* Based on clinical evidence.

† Acute diffuse pericarditis.

The electrocardiograms of these cases are illustrated in Figures 1 to 3.

The patterns upon which this study was based are: (*a*) a normal record and the normal variants, left axis shift and right axis shift; (*b*) non-specific abnormalities including intraventricular block of the

various types, A-V block, auricular fibrillation and other arrhythmias; and (*c*) he specific abnormal patterns of preponderance and infarction. The criteria for these patterns have been described in detail elsewhere.[3,7,8,21,23,24]

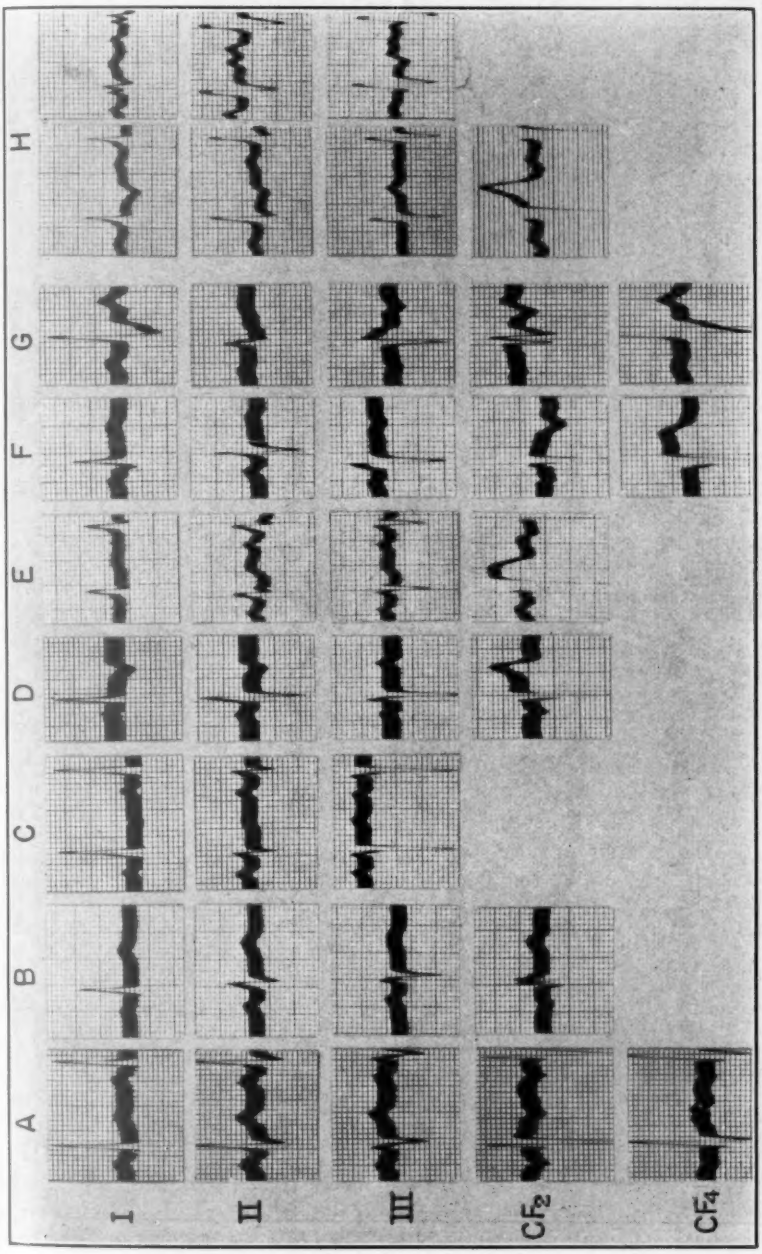

FIG. 1.—Segments of the electrocardiograms of the 8 cases in which syphilis was found at necropsy to be the sole factor leading to cardiac abnormalities responsible for electrocardiographic changes. The essential findings of these cases are summarized in Table 1. Segment *A* is Case 1; *B*, Case 2; *C*, Case 3; *D*, Case 4; *E*, Case 6; *F*, Case 7; *G*, Case 8; *H*, Case 5 (the 2 records were taken 1 month apart).

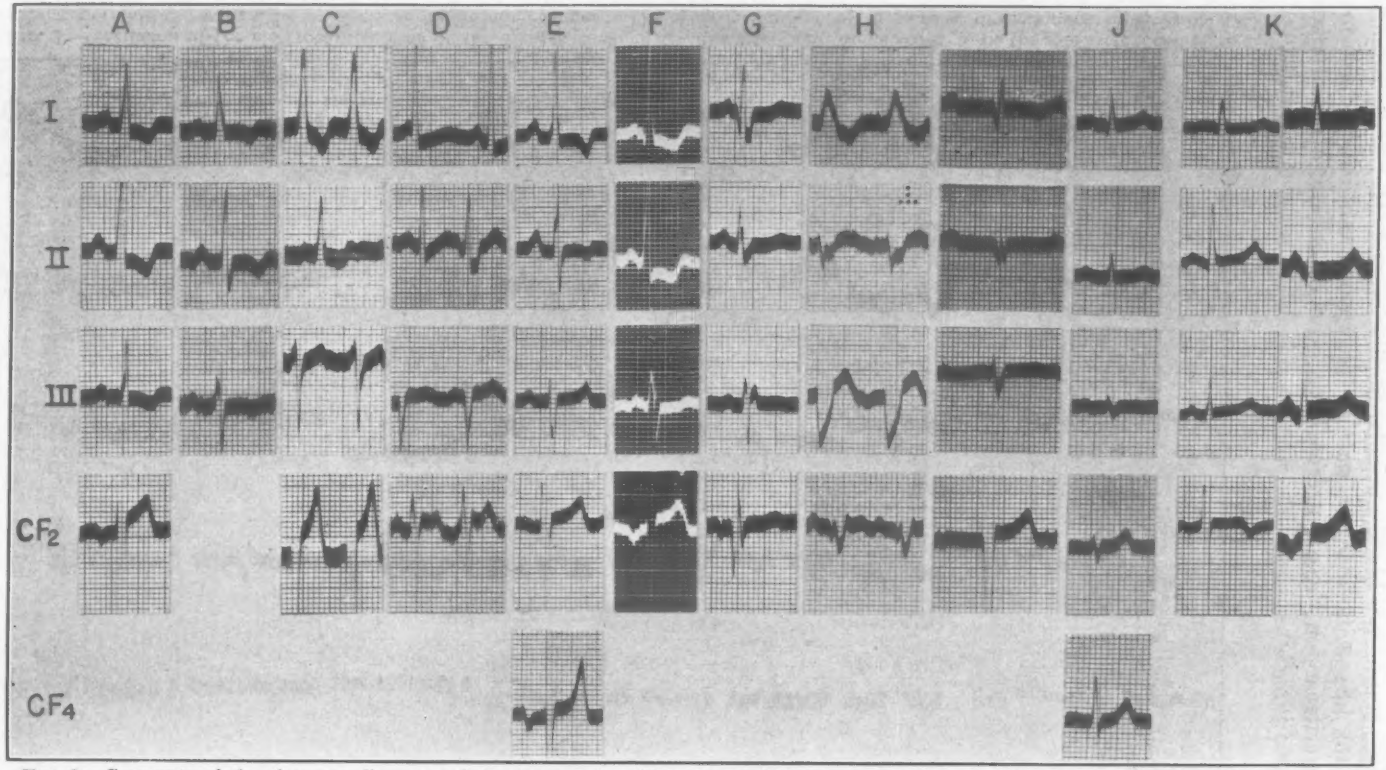

FIG. 2.—Segments of the electrocardiograms of the 11 cases in which the syphilitic anatomic abnormalities were combined with those of other etiologic factors to produce the electrocardiographic picture. The essential findings of these cases are summarized in Table 2. Segment *A* is Case 9; *B*, Case 10; *C*, Case 11; *D*, Case 12; *E*, Case 13; *F*, Case 14; *G*, Case 15; *H*, Case 16; *I*, Case 17; *J*, Case 19; *K*, Case 18 (the 2 records were taken 1 week apart).

1 week apart).

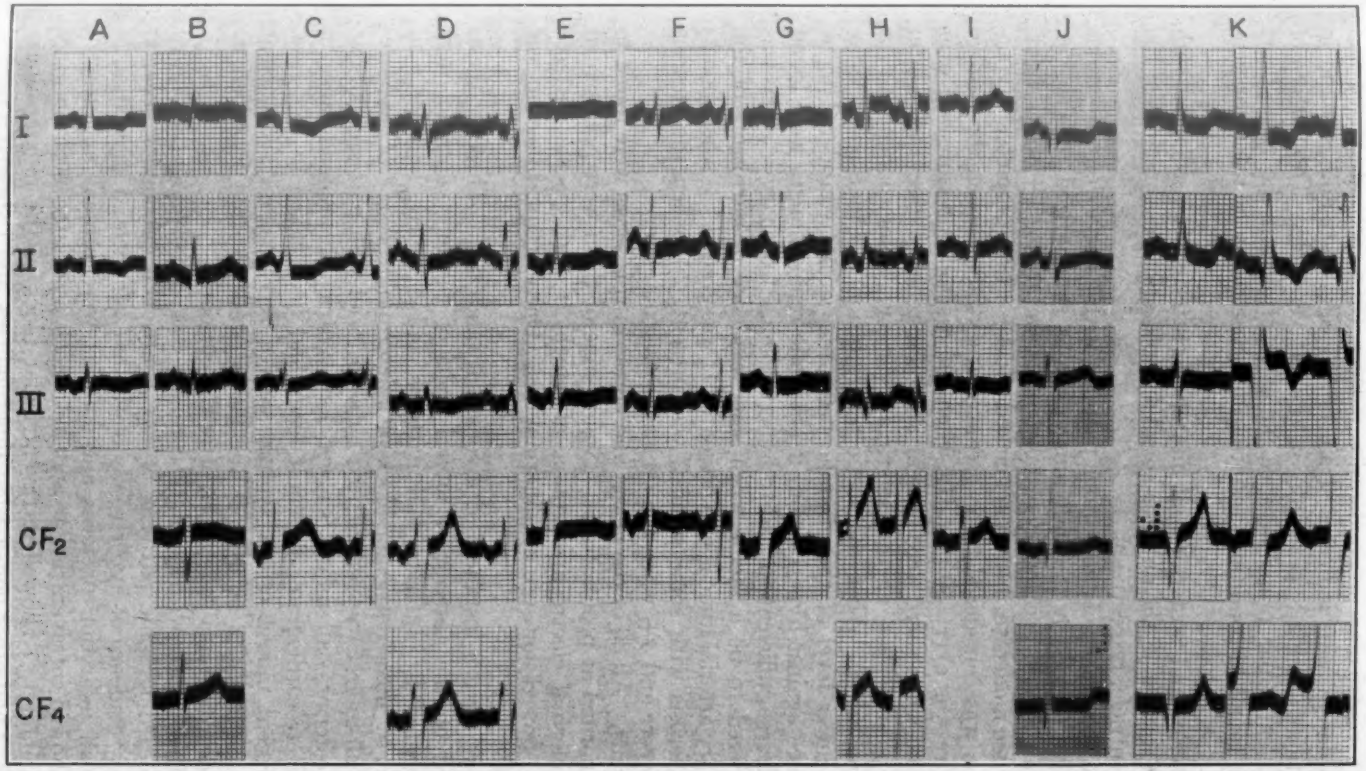

FIG. 3.—Segments of the electrocardiograms of the 11 cases in which syphilis was merely coincidental and the electrocardiographic changes were ascribed to other non-syphilitic etiologic factors. The essential findings of these cases are summarized in Table 3. Segment *A* is Case 20; *B*, Case 30; *C*, Case 22; *D*, Case 23; *E*, Case 24; *F*, Case 25; *G*, Case 27; *H*, Case 28; *I*, Case 29; *J*, Case 21; *K*, Case 26 (the 2 records were taken 11 months apart).

Left ventricular preponderance pattern (first, second, mixed and concordant types) indicates strain on the left heart and is found in conditions causing hypertrophy of the left ventricle. The pattern of right ventricular preponderance indicates strain on the right heart and is found in conditions resulting in hypertrophy of the right ventricle.

Anterior and posterior wall infarction patterns are associated with recent infarcts of the anterior-apical and posterior-basal regions of the left ventricle, respectively.

The occurrence of the various patterns with a survey of the various etiologic factors in the individual cases is summarized in Table 4. Therein, syphilitic coronary ostial stenosis was graded 1+ when slight, 2+ when moderate, 3+ when marked and 4+ when complete. Hypertension was considered to be a contributory factor when the systolic pressure was over 150 mm. Hg, when the diastolic pressure was over 100, and when there were present anatomic renal changes in the form of nephrosclerosis of the arteriolar variety, glomerulonephritis or pyelonephritis. When the aortic regurgitation was marked, a somewhat lower level of the diastolic pressure was not considered to be evidence against hypertension, if anatomic renal changes were found of a degree sufficient to lead to hypertension. Coronary sclerosis was considered to be a factor when some evidence of narrowing of the coronary arterial lumens was present. It was graded 1+ when moderate sclerosis with some stenosis was present, 2+ when the stenosis was severe and 3+ when the occlusion was complete.

Results. All 30 of the hearts and aortas in this series were found to be abnormal at postmortem. Twenty-nine of them were represented by abnormal electrocardiograms, of which 21 had specific patterns and 8 showed non-specific abnormalities. One electrocardiogram was normal.

There were 9 instances of myocardial infarction. Three of them, located on the anterior or lateral walls of the left ventricle, were represented by anterior wall patterns and a fourth anterior wall infarct by intraventricular block of indeterminate type.[9] One posterior wall infarct was represented by a posterior wall pattern, and one old posterior wall infarct showed left ventricular preponderance in the electrocardiogram; no chest leads had been taken in this case. One recent infarct of the septum showed A-V and intraventricular block. Finally, 2 infarcts of the lateral wall occurred in which no electrocardiograms were taken after the episode.

Of the 16 cases with syphilitic coronary ostial involvement, 7 showed electrocardiographic patterns of left ventricular preponderance and autopsy evidence of hypertrophy of the left ventricle; 3 showed anterior wall infarction patterns and infarcts were present at autopsy. One showed intraventricular and A-V block associated with an early septal infarct, 1 showed intraventricular block of the indeterminate S type, 3 had other non-specific abnormalities, and 1 showed a normal curve.

Aortic regurgitation was present in 19 cases. The electrocardiogram in 11 of these showed left ventricular preponderance and necropsy revealed left ventricular hypertrophy; 3, with myocardial infarcts, showed infarction patterns; 4 had non-specific abnormalities; and 1 was normal.

There were 28 cases of cardiac hypertrophy. The criteria for hypertrophy were based on findings in excess of the values given by Saphir[34] for normal hearts. The standards for left ventricular hypertrophy were heart weights in excess of 300 gm. and 250 gm. in the male and female, respectively, associated with left ventricular thickness of over 10 mm. The standard for right ventricular hypertrophy was a right ventricular thickness of over 3 mm. with similar heart weights.

In 25 of the 28 cases of cardiac hypertrophy, the left ventricle was involved, solely or predominantly. Left ventricular preponderance was present in the electrocardiograms of 14 of these cases, infarction patterns associated with infarcts were present in 3. Intraventricular block was present in 3, other non-specific abnormalities were found in 4 and a normal electrocardiogram occurred in 1 of these. In 2 of the cases in which the left and right ventricles were both hypertrophied to an approximately equivalent extent, 1 was represented by a left and the other by a right ventricular preponderance. In 1 case of hypertrophy of only the right ventricle, the electrocardiogram revealed right ventricular preponderance.

The chief concomitant factors encountered were coronary sclerosis, which was of sufficient degree in 12 cases to affect the electrocardiogram, and hypertension, which was present in 10 of the cases. Mitral endocarditis (rheumatic), bronchiectasis, tuberculosis, emphysema, a stab wound of the heart, vitamin B deficiency were also encountered and found to influence the electrocardiogram.

Discussion. The specific electrocardiographic patterns occurring most frequently in this series were left ventricular preponderance in 15 cases, and anterior wall infarction in 3 cases. Two of the 3 anterior wall patterns were associated with recent infarction due to syphilitic coronary ostial stenosis alone (Cases 6 and 7). The 3rd (Case 17) was due to a combination of syphilitic and coronary sclerotic processes.

The incidence of 9 myocardial infarctions in this series is high. A survey of the literature of the past 10 years revealed reports of only 12 cases of anatomically demonstrated myocardial infarction due solely to syphilitic coronary ostial stenosis[11,12,13,29,34] and in none of them were electrocardiograms shown or described. In 3 of the cases in the present series (Cases 6, 7 and 8) the infarct was on a purely syphilitic basis; in 3 others (Cases 10, 15, 17) the infarct was due to syphilitic stenosis and coronary sclerosis combined; and in the remaining 3 (Cases 23, 26, 27) the infarct was due to coronary sclerosis alone.

The frequency of coronary sclerosis complicating coronary ostial stenosis is one reason infarction attributable to syphilitic ostial encroachment, alone, is relatively rare. This, however, is not the sole

explanation. Usually encroachment of the coronary orifices by syphilis is such a gradual and slowly progressive process that the collateral circulation is able to keep pace with the occlusive mechanism. It is only in those cases in which this fails that infarcts develop. Apparently this latter circumstance is the more unusual in syphilis. In 1 case a coronary embolus arising from the wall of a syphilitic aorta resulted in an anterior wall infarction pattern, the patient succumbing too soon, however, for the characteristic morphologic changes of infarction to appear at postmortem examination.[32]

The second of the specific patterns frequently found, left ventricular preponderance, was present in 15 cases. There were 8 examples of the second type, 4 of the mixed and 3 of the concordant types. There were no instances of left preponderance of the first type in which axis deviation occurred without S-T-T abnormalities. This and the absence of axis deviation in one-fifth of the cases emphasizes again the importance of the S-T-T changes in the recognition of the preponderance pattern. Syphilitic lesions, aortic regurgitation, and coronary ostial stenosis were responsible in whole or in part for the left ventricular strain in 11 of the cases.

Aortic regurgitation operates by increasing the work of the left ventricle. It causes dilatation and eventually hypertrophy of that chamber. Syphilitic coronary ostial stenosis[12,34] has also been found to cause moderate hypertrophy, especially of the left ventricle, although usually not to the extent found in regurgitation. The two lesions were found to occur together so frequently that the rôle of each was difficult to ascertain. In Case 1, however, the hypertrophy of the left ventricle and the left ventricular preponderance could be attributed to syphilitic aortic regurgitation, *per se*.

The frequency of the specific anterior wall infarction and left ventricular preponderance patterns is greatest among the cases in which syphilis was the sole etiologic factor (Table 4). In the cases in which syphilis and other factors were combined, more non-typical patterns appear. Non-specific abnormalities occur with greatest frequency in the group of cases in which syphilis was merely a coincidental finding as far as the electrocardiographic contour was concerned.

Before the electrocardiogram in syphilitic cardiovascular disease can be properly evaluated, the extent and effect of concomitant disease factors must be determined, since they may produce similar findings, and in some cases superimpose typical patterns of their own. Thus hypertension and arteriosclerosis[15,18,25,30,36] which have been found to produce cardiac hypertrophy, caused the left ventricular preponderance patterns in Cases 20, 21, 22 and combined with syphilitic aortic regurgitation to produce them in Cases 9 to 14. Coronary sclerosis leading to posterior wall infarction dominated the electrocardiogram in Case 26 which had formerly shown a left ventricular preponderance pattern attributable in part to syphilitic aortic regurgitation. Mitral stenosis might have counteracted the tendency of syphilitic aortic regurgitation and coronary ostial stenosis to produce left preponder-

ance pattern in Case 18, and resulted in a right ventricular preponderance pattern in Case 25.

Of the various individual syphilitic lesions, it is apparent that syphilitic aortitis in itself does not affect the electrocardiogram. None of the 13 instances of aneurysm of the aorta and innominate arteries could be demonstrated to affect the electrocardiogram either because of situation or complication. There have been a few instances of complications of aneurysms recorded, however, such as an increase in the size and the position of the aneurysm which caused a change in position of the heart with resultant axis deviation,[16] an instance of aortic aneurysm rupturing into the pulmonary artery,[37] or into the pericardial sac[35] giving rise to a hemopericardium and an electrocardiographic pattern of acute diffuse pericarditis.

The rôle of syphilitic aortic regurgitation in the production of left ventricular preponderance patterns has been discussed above.

Coronary ostial stenosis may produce the specific pattern of left ventricular preponderance by leading to left ventricular hypertrophy or it may cause myocardial fibrosis for which there is no specific pattern. As the specialized conducting tissues of the heart are deprived of their blood supply by this occlusive process, A-V and intraventricular block appear. Thus in Case 5, the left ventricular preponderance due to aortic regurgitation and coronary ostial stenosis was later replaced by intraventricular block when the blood supply to the bundle branch system was affected. Mahaim[28] recognized the relationship of syphilitic ostial occlusion to intraventricular block. It is possible, however, that massive increase in heart size with the resulting relative coronary insufficiency on occasion may lead in syphilis, as in other circumstances, to broadening of the QRS span.

When, in bilateral involvement of the coronary orifices, complete obliteration of the right coronary ostium was present, conduction defects appeared in Cases 5 and 8, while, when the left coronary ostium was markedly narrowed, infarction of the anterior wall type resulted (Cases 6 and 7).

Diffuse syphilitic myocarditis and gummatous lesions were not encountered in this series.

Summary and Conclusions. The electrocardiograms and postmortem findings of 30 cases of cardiovascular syphilis are presented and correlated in each case. For this purpose the electrocardiographic tracings were divided into several specific patterns, the criteria for which have been established.

All 30 of the hearts and aortas in this series were found to be abnormal at postmortem. In 8 the anatomic findings and resulting electrocardiographic tracings were entirely on a syphilitic basis. In 11 other cases, syphilitic anatomic abnormalities were combined with those of other etiologic factors to produce the electrocardiographic pattern. The remaining 11 cases manifested syphilitic lesions as coincidental findings; the electrocardiographic contours being ascribed to the non-syphilitic lesions.

Although no specific pattern was found to be pathognomonic of syphilitic cardiovascular disease, two specific patterns occurred frequently due in whole or in part to syphilis. There were 11 cases of left ventricular preponderance and 3 cases of anterior wall infarction pattern.

The frequency of left ventricular preponderance and anterior wall infarction patterns was greatest in the cases having syphilis only, whereas, non-specific electrocardiographic abnormalities appeared when concomitant disease elements were present and non-typical patterns predominated when the latter were dominant.

Uncomplicated syphilitic aortitis, *per se*, and uncomplicated aneurysms caused no electrocardiographic abnormalities.

Aortic regurgitation produced left ventricular hypertrophy, reflected by various types of left ventricular preponderance in the electrocardiogram.

Coronary ostial stenosis in some instances caused myocardial fibrosis which has no specific electrocardiographic pattern. Stenosis of the mouths of the coronary arteries was shown to contribute to the formation of cardiac hypertrophy, especially of the left ventricle, resulting in left ventricular preponderance patterns electrocardiographically.

When localized areas of the myocardium were deprived of their blood supply by coronary ostial encroachment, corresponding specific infarction patterns were present in the electrocardiogram. These were all of the anterior wall type in our series.

When the septum and conducting system were similarly deprived of their blood supply, the electrocardiogram showed A-V and intraventricular block.

While the absence of electrocardiographic change does not rule out cardiovascular syphilis, most cases of far-advanced syphilis have abnormal electrocardiograms.

The presence of the special patterns of left ventricular preponderance and anterior wall infarction in cases of cardiovascular syphilis uncomplicated by other diseases is a good index, respectively, of hypertrophy of the left ventricle and myocardial infarction of syphilitic origin.

We are grateful to Dr. O. Saphir for permission to use his postmortem findings in these cases as the basis of the study; to Dr. R. Langendorf for his suggestions and criticisms and to Dr. L. N. Katz, under whose guidance this work was done, for his advice in carrying out the study. Some preliminary data was gathered for this study by Dr. Harold Engle before he left for service with the Army Air Forces.

ADDENDUM:—In a report appearing after this communication was in press, Evan Jones and D. Evan Bedford (Brit. Heart J., **5**, 107, 1943) cited 12 necropsied cases. All of them had aortic regurgitation and 10 had coronary ostial stenosis resulting from syphilis. The electrocardiograms in 10 were abnormal. However, the electrocardiograms were not shown and the detailed findings in the individual cases were not given.

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THE PATHOLOGIC CHANGES IN SULFADIAZINE INTOXICATION*

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Numerous experimental and clinical reports indicated the great therapeutic value of the new sulfonamide drug, sulfadiazine, in various bacterial infections. Furthermore, early clinical trial showed a lower

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degree of toxicity for this preparation, elaborated by Roblin and his co-workers, than with other sulfonamide compounds. The need for such a drug led to its widespread use in military and civilian practice. With this extensive application reports appeared in the literature of serious and sometimes fatal toxic effects. The majority of the clinical and pathologic studies stressed the urinary complications, particularly crystalluria and secondary mechanical renal trauma and blockage. Toxic damage to other organs or systems was recognized, also, but the incidence was much less and histopathologic examinations were infrequent because most patients recovered. The purpose of this report is to present the pathologic findings in 3 fatal cases, treated with sulfadiazine for streptococcic infections. In the first 2 patients severe organic damage was encountered; the 3rd case is presented as a control to illustrate the normal tissue reactions to sulfadiazine. Complete autopsies were performed.

Case Studies. CASE 1. V. K., white male, age 28; streptococcic nasopharyngitis, increasing toxemia, coma, cyanosis, fever up to 106.2° F., death on the 13th hospital day. This patient was admitted to hospital on Jan. 1, 1943. He complained of generalized aches and pains and sore throat of 1 weeks duration. Past personal history was negative, except for pneumonia in 1932 with uneventful recovery. Admission examination: temperature 102° F., pulse 104, respiration 22 per minute. The mucosa of the nasopharynx was hyperemic; the tonsils had been removed. Both anterior cervical lymph node chains were moderately enlarged. The chest examination revealed only a few coarse râles over the main bronchi.

A throat specimen was taken for smear and culture and routine upper respiratory treatment was instituted. Sulfadiazine was administered with an initial dose of 3 gm. followed by 1 gm. every 4 hours. Other treatment included bed rest, fluids, gargles and codeine cough syrup.

Laboratory Reports. Throat cultures positive for a non-hemolytic streptococcus on admission and on 2 subsequent examinations. *Urinalysis* negative on Jan 4 and 9, 1943. *Blood:* red cells 5,180,000, hemoglobin 16.7 gm., white cells 7800 (68% polymorphs, 30% lymphocytes, 2% eosinophils). *Chest Roentgen ray:* on Jan. 10, 1943: "No infiltration in either lung field. There is slight elevation of the right diaphragm."

Clinical Course. Within a few days after admission the patient's condition was much improved and an uneventful recovery was expected. However, on Jan. 9, 1943 a generalized purpuric skin eruption appeared. Sulfadiazine was stopped and fluids were forced. The 24 hour fluid intake on January 8 was 3100 cc., the urinary output 1050 cc. The temperature at this time was 102.6° F., pulse 102, respirations 23 per minute. A total of 45 gm. of sulfadiazine had been given up to the time of the eruption. During the next 36 hours the clinical course became stormy: the temperature rose to 106.2° F.; severe dyspnea, cyanosis, mental confusion and restlessness developed.

Additional Laboratory Studies. Blood: free sulfadiazine level 5.7 mg. per 100 cc.; white cell count 14,900 (93% polymorphs, 6% lymphocytes, 1% basophils); non-prot. N, urea N and sugar normal. *Icteric index* 11. *Urinalysis:* negative.

LEGENDS FOR FIGS. 1 AND 2.

FIG. 1.—Spleen. Two Malpighian corpuscles are seen. The lymphocytes around the central arteriole are almost completely absent. Cellular débris, nuclear fragments and infiltrating polymorphonuclear leukocytes are apparent in this region. (200 ×.)

FIG. 2.—Liver. Marked fatty metamorphosis is observed and all parts of the lobule are affected. (60×.)

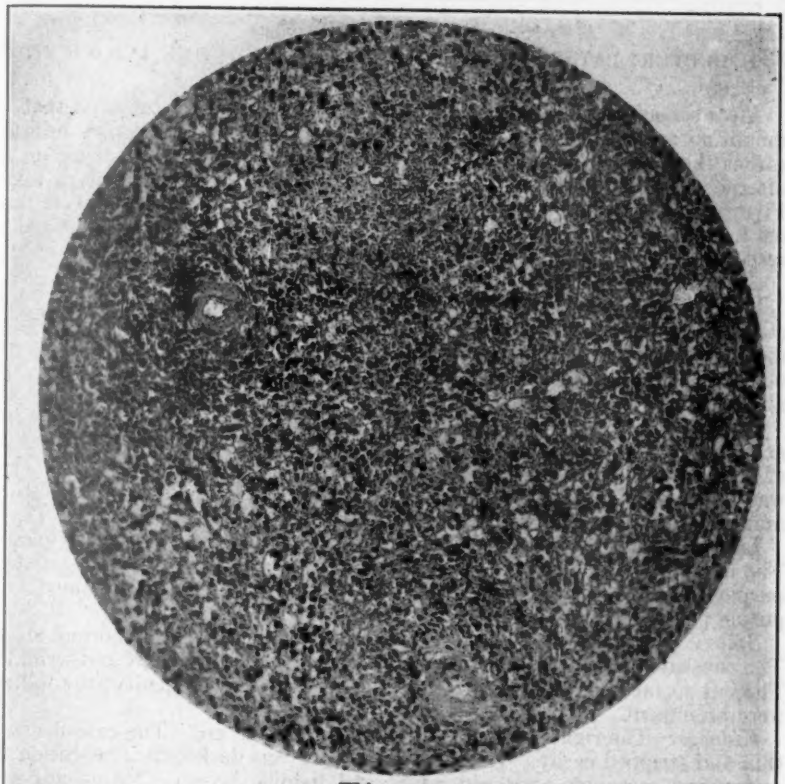

Fig.1

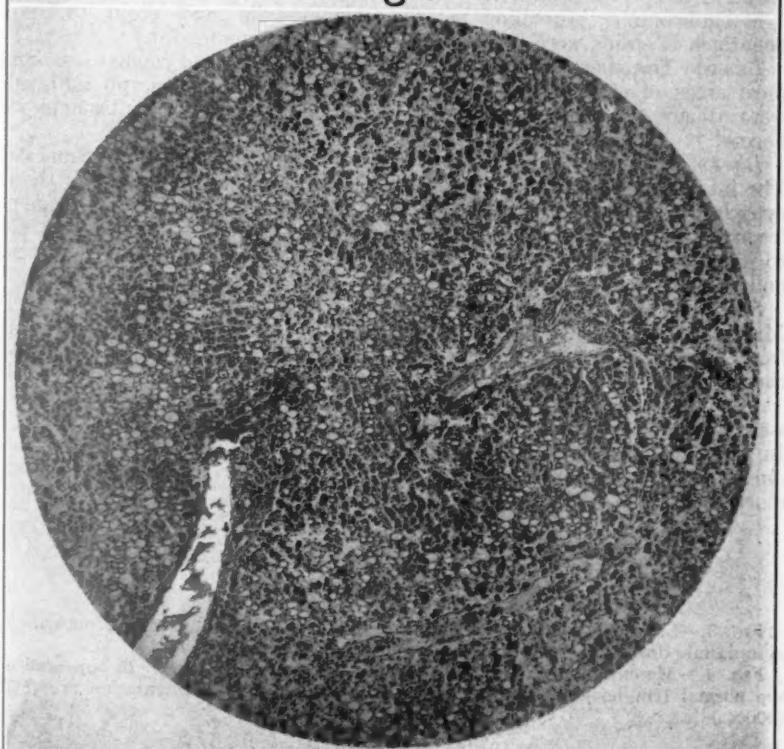

Fig.2

After consultation the sulfadiazine was resumed. It was believed that the mounting toxemia was secondary to the original upper respiratory infection rather than to sulfadiazine. The drug was readministered beginning on the afternoon of January 10 in 1 gm. doses every 4 hours; 14 gm. were taken. Five per cent glucose solution and blood plasma were given in 500 cc. doses on the same days. Oxygen was given by mask. The patient showed no response, lost consciousness and died on Jan. 13, 1943.

Autopsy Abstract. (2 hours after death):

GROSS. The body was that of a well-developed, well-nourished young adult male, weighing 184 pounds and measuring 67 inches. The mucous membranes of the mouth were dry, crusted and extremely cyanotic. Numerous petechial and purpuric hemorrhages were present in the skin over the abdomen and lower extremities.

Lungs: The right weighed 435 gm., the left 480 gm. Dark purple congestion and slightly decreased crepitation were found in the dependent parts of both organs. The cut surface of each lung oozed frothy, bloody fluid; there was no consolidation. The bronchi contained a moderate amount of thick mucoid sputum. The blood-vessels were intact.

Liver: Weighed 2100 gm. The capsule was smooth, thin and transparent. The underlying parenchyma appeared yellow to orange with irregular patchy purple congestion. The cut surface was yellowish tan and contained faint purple patches. The vascular and biliary branches were normal.

Spleen: Weighed 315 gm., was moderately enlarged and of normal shape. The consistency was firm. The capsule was thin, purplish gray and wrinkled. The cut surface appeared reddish purple, scraped with difficulty; the follicles were prominent.

Kidneys: The right weighed 170 gm., the left 175 gm. The capsules were thin and stripped easily. The external surface was dark red. On section the cortex and pyramids appeared intact and reddish brown. No calculi were found in the pelves or ureters.

MICROSCOPIC. (Formalin, paraffin, hematoxylin and eosin technique. Scharlach R stains were performed on frozen sections for fat.)

Lungs: The alveolar walls were markedly congested and edematous. Small focal areas of atelectasis with slight round cell and polymorph infiltration were apparent. There was no pneumonia. The vessels and bronchi were normal.

Liver: Marked fatty metamorphosis was present in the parenchymal cells. The fat was distributed in the form of coarse or fine droplets within the cell cytoplasm; in cells with coarse droplets the nuclei were pushed to the side and frequently appeared pale and vesicular. Some nuclei were enlarged, almost to giant proportions. The sinusoids were narrowed. Moderate hyperemia and polymorph infiltration were apparent in the periportal regions.

Spleen: Striking focal necrosis of the lymphoid cells was present in the Malpighian corpuscles (Fig. 1). This destruction of lymphoid collars varied from partial to complete, with abundant basophilic cellular débris, hemorrhages and occasional polymorphs in these areas.

Lymph Nodes. Mesenteric: The lymphoid follicles throughout the node were markedly necrotic; the changes were similar to the picture in the spleen. In these foci basophilic fibrinous débris, including pyknotic and fragmented nuclei, was abundant. The margins were hyperemic, infiltrated by polymorphs and contained occasional thrombosed vessels.

LEGENDS FOR FIGS. 3 AND 4.

FIG. 3.—Liver. Almost every liver cell in the field shows fatty metamorphosis. The cytoplasmic droplets vary in size, some coarse, many fine. (200×.)

FIG. 4.—Mesenteric lymph node. Marked necrosis with partial disappearance of the normal lymphocytes is noted. Nuclear pyknosis and fragmentation are severe. (200×.)

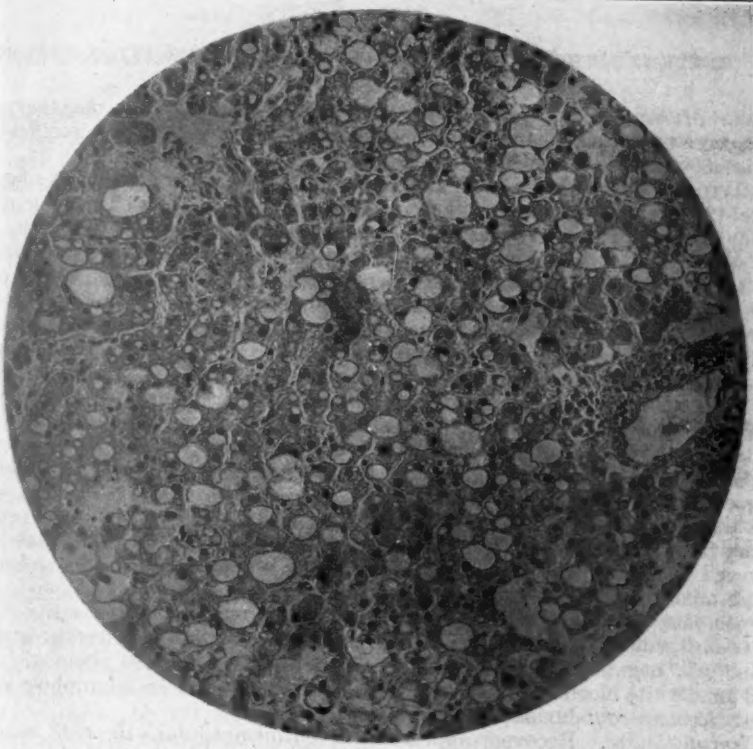

Fig. 3

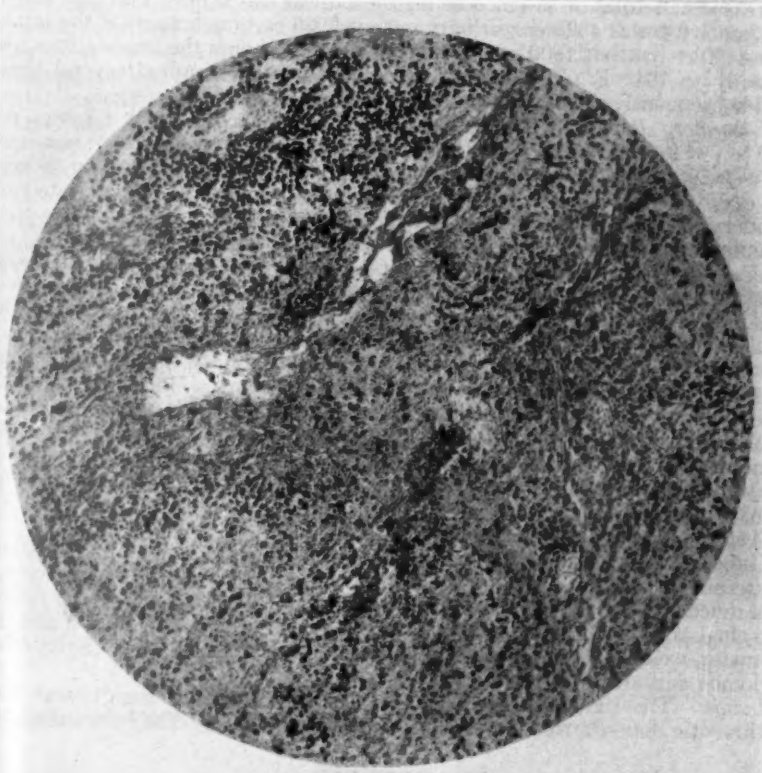

Fig. 4

Bone Marrow. Ribs: Hematopoiesis was very active. The megakaryocytes were numerous: as many as 12 were apparent in some high-power fields. No areas of necrosis were seen.

ANATOMIC DIAGNOSES. (1) Fatty metamorphosis of liver, severe, acute, toxic; (2) focal necrosis of spleen and mesenteric lymph nodes, moderate, acute, toxic; (3) acute passive congestion of lungs and abdominal viscera, severe.

CASE 2. L. M., white male, age 34; streptococcic nasopharyngitis, mounting toxemia, dyspnea, cyanosis, temperature to 105.8° F., coma, death on 13th hospital day. This patient was admitted to hospital on Jan. 1, 1943; he was a companion of Case 1. The complaints were sore throat, chills, fever and a tight feeling in the center of the chest, all present for 4 days. He had measles and scarlet fever in childhood. Admission examination: temperature 102° F., pulse 80, respirations 20 per minute. The nasopharyngeal mucosa was hyperemic and was covered with abundant mucopurulent exudate in the posterior pharynx. Anterior and posterior cervical lymph node chains were palpable. Heart was negative. The lungs were normal except for a few coarse râles over the main bronchi.

A throat specimen was taken for smear and culture and routine upper respiratory treatment was started. This included sulfadiazine, 3.0 gm. immediately, followed by 1 gm. every 4 hours. Fluid intake was encouraged and codeine cough mixture was administered as required.

Laboratory Reports. Throat Culture: Admission culture was positive for *S. viridans;* cultures on January 7 and 11 revealed non-hemolytic streptococcus. *Urinalysis* negative. *Blood:* January 2, red cells 5,720,000, hemoglobin 17.3 gm.; white blood cells 6600 with 52% polymorphs and 48% lymphocytes. *Chest Roentgen ray:* January 2, normal.

Clinical Course. Recovery appeared uneventful until Jan. 10, 1943, when dull pain developed in the right lumbar region and a skin eruption, identical with that in Case 1, was noted. Sulfadiazine was stopped and the fluid intake increased. A total of 33 gm. was ingested up to this time. The fluid intake on January 6 was 4525 cc.; urinary output 2925 cc.; on January 8 the intake was 4400 cc., output 1800 cc. During the next 72 hours the temperature rose steadily to 104° F. The patient became nauseated, vomited several times and subsequently developed cyanosis, dyspnea and restlessness.

Laboratory Report at This Time. Blood: Sulfadiazine level 4.3 mg. per 100 cc.; white cell count 11,900 (92% polymorphs, 8% lymphocytes); non-prot. N, urea N and sugar normal. Icteric index 11. *Urinalysis:* albumin 30 mg.; no casts or red blood cells; no crystals. *Chest Roentgen rays* repeated on January 10, 12 and 13, and showed no significant change from the early examination except for some elevation of the right leaf of the diaphragm.

Consultation was obtained. The unfavorable turn in the clinical course was interpreted as secondary to recrudescence of the original respiratory infection rather than from sulfadiazine toxemia. The sudden deterioration in the clinical condition of both patients seemed to coincide with the withdrawal of the drug. Therefore, sulfadiazine was resumed on January 10, with the dosage of 1 gm. every 4 hours, so that an additional amount of 16 gm. was taken. The treatment was supplemented with 5% glucose solution intravenously in 1000 cc. doses on January 10 and 11, 500 cc. of plasma intravenously on the same days and oxygen by mask. There was no response. The temperature continued to rise and on January 10 reached 105.4° F. The patient became comatose, and died on Jan. 13, 1943.

Autopsy Abstract. (12 hours after death):

GROSS: The body was that of a well-developed and well-nourished adult white male, weighing 156 pounds and measuring 65 inches. The nasopharyngeal mucous membranes were markedly cyanotic. Numerous fresh and fading petechial and purpuric hemorrhages, which varied in size from 1 to 3 mm. in diameter, were scattered in the skin and were most numerous over the anterior abdomen and lower extremities.

Lungs: The right weighed 610 gm., the left 325 gm. Small, scattered anthracotic deposits were present in the visceral pleura. The lung substance

was reddish gray anteriorly, with purplish mottling in the dependent portions. The latter were doughy and in some regions edematous. The cut surface oozed bloody fluid, was purplish red due to hypostatic congestion. The blood-vessels were normal. The bronchial mucosa appeared diffusely cyanotic.

Liver. Weighed 1760 gm., was slightly decreased in size and of normal shape. The capsule was thin and transparent. The parenchyma was yellowish brown with scattered purpuric hemorrhages. The consistency was soft and somewhat mushy. The parenchyma in the cut surface appeared yellowish to orange-brown and contained small purpuric hemorrhages. Mild passive congestion was distinguished in some parts. The vascular and biliary branches were normal.

Spleen: Weighed 425 gm., was enlarged in size and of normal shape. The capsule appeared thin, purplish gray and wrinkled. The cut surface was dark purple, firm, and scraped with some difficulty; the follicular markings were fairly distinct.

Kidneys: The right weighed 150 gm., the left 145 gm. The capsules were thin, stripped easily; the external kidney substance was reddish brown. The cut surface was moderately congested, the cortex reddish brown, the pyramids purplish brown. No concretions were found in the pelves or ureters. There were a few scattered petechiæ in the pelvic mucosæ.

Microscopic. *Lungs:* The alveolar walls were hyperemic, edematous and, in scattered fields, were mildly infiltrated by polymorphs and round cells. Some alveoli were collapsed; none of the alveolar lumens contained exudate. The arteries were normal. In several bronchi the lining epithelium was exfoliated and small foci of fibrinoid necrosis were visible in the submucosa. Round cells, polymorphs and nuclear débris were observed in the centers and margins of the necrotic foci.

Liver: All fields displayed disorganization of the normal structure and severe fatty metamorphosis. Almost all liver cells were affected. Some contained large fat droplets in the cytoplasm with eccentric displacement of the nucleus; in others the droplets were fine and distributed through the cytoplasm. A few areas were almost completely devoid of liver cells; here, only scattered nuclear shadows remained in an edematous background. The periportal regions were moderately infiltrated by round cells and polymorphs (Figs. 2 and 3).

Spleen: Widespread hyperemia and edema were present in the pulp. Focal fibrinoid necrosis was apparent in the lymphoid elements of the Malpighian bodies; in such necrotic zones disappearance or reduction in number of the lymphocytes was associated with much fragmented nuclear débris. Many lymphocytic nuclei were pyknotic; scattered polymorph infiltration was present along the margins of focal necrotic areas.

Lymph Node—Mesenteric: Focal and diffuse fibrinoid necrosis was observed. In such foci the cortical nodules were destroyed. Basophilic cellular débris and pyknotic and fragmented nuclei were prominent. The lymphocytes were decreased, absent in some fields, and the stroma hyperemic. Many small vessels were thrombosed. Polymorph infiltration was present throughout (Fig. 4).

Kidneys. The stroma was moderately hyperemic; the arteries appeared slightly thickened. The arterioles and glomeruli were intact. There was a small amount of pale staining, granular débris in the lumens of the proximal convoluted tubules; the tubular epithelium appeared cloudy and swollen.

Bone Marrow. The fatty stroma was moderately edematous and the cellular elements were composed predominantly of erythrocytes and granulocytes in all stages of development. The ratio appeared normal. Marked megakaryocyte activity could be distinguished.

Anatomic Diagnoses. (1) Fatty metamorphosis of liver, severe, acute, toxic. (2) Focal necrosis of spleen and mesenteric lymph nodes, moderate, acute, toxic. (3) Acute, passive congestion of lungs and abdominal viscera, severe. (4) Acute, focal, necrotizing bronchitis, mild.

CASE 3. H. R., white male, age 50; left peritonsillar abscess, cavernous sinus thrombosis, suppurative meningitis, brain abscesses, right hemiplegia, pneumonia, fever to 108° F., death on 13th hospital day. This case is reported as a control in the sense that it illustrates the relative harmlessness of the drug in a non-susceptible individual. The patient received intensive sulfadiazine treatment, much of it intravenously; the amount ingested and the free sulfadiazine blood level were much higher than in Cases 1 and 2.

The patient was admitted to hospital on Feb. 19, 1943, by transfer from a station hospital. The temperature was 103° F. and the patient was somewhat confused mentally. His complaints were chiefly difficulty in swallowing and pain in the right temple. There had been severe pain in the left side of the face on February 17, but this had subsided by the time of admission.

Physical examination revealed a left peritonsillar abscess, which was incised immediately and a large quantity of thick yellow pus was evacuated. On the following morning his condition seemed improved but on the next day inflammation and proptosis developed in the right eye and the temperature rose to 103° F. The diagnoses of cavernous sinus thrombosis and meningitis were made and oral and intravenous treatment with sulfadiazine was undertaken. The course was steadily retrogressive; hypostatic pneumonia developed on February 27, and right hemiplegia on March 2. Death occurred on March 3, 1943.

The sulfonamide treatment included: sulfathiazole 20 gm. in 5 days before entering Fitzsimons; sulfadiazine 62.6 gm. (17 gm. intravenously) in 11 days at Fitzsimons. The average blood level of free sulfadiazine was 15 mg. per 100 cc. (the lowest 4.4 mg.; the highest 20.4 mg.).

Autopsy (16 hours after death):

GROSS. The body was that of a well-developed and fairly well-nourished middle-aged white male, weighing 135 pounds and 71½ inches in length. Generalized purple mottled discoloration was present in skin. The right orbital soft tissues were edematous, congested; there was a 0.7 cm. recent surgical incision at the upper internal angle. *Intracranial examination* revealed an acute generalized suppurative pachymeningitis and leptomeningitis; acute, suppurative thrombophlebitis in the left pterygoid plexus, in both cavernous sinuses, in the circular sinus, in the upper petrosals and in the right ophthalmic vein; multiple brain abscesses.

Lungs: The right weighed 860 gm., the left 815 gm. The visceral pleura was thin and glistening. Each lung appeared bright red anteriorly, purplish red in its dependent portion. The substance was edematous and airless posteriorly, doughy elsewhere. Emphysematous bullæ were present along the fringes. The cut surface was congested, moist, and oozed bloody fluid on pressure. Dark purple areas were distinguished in the dependent regions. The bronchi contained a moderate amount of opaque white fluid, which appeared to be aspirated milk.

Liver: Weighed 2680 gm., was enlarged, soft and of normal shape. The capsule was thin and transparent. The parenchyma was mottled purplish red to purplish yellow. The cut surface was purplish red with irregular yellowish brown areas. Moderate passive congestion was seen.

Spleen: Weighed 235 gm., was moderately enlarged, soft and normal in configuration. The capsule was thin, wrinkled and purplish red. The cut surface was deep purple, scraped easily; the follicular markings were indistinct.

Kidneys: The right weighed 185 gm., the left 215 gm. The capsules were normal. The external surfaces were purplish red, contained scattered, small, depressed stellate scars and a few sharply demarcated, bright yellow adenomatous nodules, the largest 0.6 cm. in diameter. The cut surfaces of the kidneys were moderately hyperemic. No concretions were found.

MICROSCOPIC. *Brain and Meninges:* The leptomeninges were hyperemic and infiltrated by polymorphs and round cells. Exudate composed of fibrin, polymorphs and bacteria filled the subarachnoid space, particularly in the sulci and over the base. Many acute abscesses were scattered through the brain; their centers contained polymorphs, necrotic brain tissue, bacteria and cellular

débris; their margins were hyperemic with an occasional thrombosed vessel therein. Some vessels were ringed by polymorphs.

Lungs. Lobular inflammatory zones, some peribronchial, were present in the parenchyma. In these areas the alveolar capillaries were hyperemic and the bronchioles and alveolar lumens filled with fibrin, polymorphs and occasional red cells. The vessels elsewhere were not noteworthy.

Liver: Mild fatty changes were observed in the parenchyma; in some fields the liver cells adjoining the periportal region were involved; in others, those centrally located were affected. Moderate round cell infiltration was present in the interlobular trabeculæ. Moderate passive congestion and cloudy swelling were observed.

Spleen: The Malpighian corpuscles appeared hyperplastic and the sinusoids were distended, congested and contained numerous polymorphs.

Lymph Nodes—Peribronchial: Acute hyperemia was noted; in some fields hemorrhage and polymorph response to the bronchiolar pneumonia could be distinguished. There was no necrosis of lymphoid tissue.

Bone Marrow: The stroma was hyperemic, edematous, in parts slightly hemorrhagic. Hematopoiesis was active; the erythromyeloid ratio appeared normal. The megakaryocytes were increased in number, with as many as 15 visible in some low-power fields.

Kidneys: The yellow nodules were cortical adenomata of adrenal type. The remaining parenchyma was hyperemic. Scattered small superficial scars were present in the surface zone of the cortex. The tubules contained small amounts of acid-staining granular débris.

Bacteriologic Examination (Post mortem): Cultures of exudate from the brain abscesses and meninges were positive for non-hemolytic streptococcus.

Anatomic Diagnoses: (1) Peritonsillar abscess, left, severe. (2) Acute, suppurative thrombophlebitis of left pterygoid plexus, of cavernous sinuses, of circular and upper petrosal sinuses, and of right ophthalmic vein. (3) Acute, suppurative leptomeningitis and pachymeningitis, severe. (4) Multiple brain abscesses, acute. (5) Mixed hypostatic and aspiration pneumonia, bilateral, severe. (6) Fatty metamorphosis of liver, mild, acute. (7) Multiple cortical adenomata of kidneys, bilateral adrenal type.

Comment. *Liver.* The accumulated evidence of toxic sulfonamide effects on the liver of susceptible individuals is so conclusive that no detailed reference to the literature is necessary. Sulfadiazine appeared to be less dangerous in this respect. Finland, Peterson and Goodwin[5] found no instance of hepatitis in 460 patients treated with it. In fact, 6 patients with severe liver damage in their series showed improved liver function during administration of sulfadiazine. On the other hand, Cantarow and Wirts[2] in a smaller group of 20 patients obtained results which pointed to hepato-cellular changes. They performed liver function tests during treatment with sulfadiazine and related drugs. No tissue studies were made.

The pathologic alterations described in Cases 1 and 2 consisted of marked diffuse fatty changes, which are designated usually as fatty metamorphosis. Such fatty alterations are observed in varying degrees in chronic alcoholism, benzene or chloroform poisoning and pulmonary tuberculosis. In the first 2 patients this was one of the important anatomic findings and its relation to the sulfadiazine treatment appears unquestionable. Neither patient received yellow fever vaccine previously. Undoubtedly the process caused impairment of liver function but never to the point of clinical jaundice.

In contrast to the liver damage in the first 2 patients, Case 3, H. R.,

showed only mild alteration which was of similar fatty character. Attention has been directed repeatedly by others to the lack of correlation between the dosage of sulfonamide drugs and the extent of toxic effects in susceptible persons. This is confirmed again in the cases here as shown by an analysis of the sulfadiazine dosage and blood levels. W. K. (Case 1) received 59 gm. of sulfadiazine over a period of 12 days; L. M. (Case 2) ingested 49 gm. in 9 days. The blood level was taken only once at the height of the treatment and was 5.7 mg. per 100 cc. in Case 1, 4.3 mg. in Case 2. H. R. (Case 3) was administered 20 gm. of sulfathiazole and 62.6 gm. of sulfadiazine (17 gm. sodium sulfadiazine intravenously) over 16 days and the blood level of free sulfadiazine ranged between 4.4 and 20.4 mg.; it averaged about 15 mg.

Case 3, H. R., received a greater amount of sulfonamide, most of it sulfadiazine, than either of the other 2 and his blood level was much higher. However, the liver changes were comparatively mild and probably reversible. The only significant difference in the clinical behavior of Case 3 was the absence of a skin eruption. No liver function tests were performed on any of the patients; the icteric index was slightly elevated in Cases 1 and 2.

Spleen and Lymph Nodes. Only a few studies are available concerning toxic changes in the spleen following the administration of sulfonamide drugs and the majority of these are experimental. The only report available to the author that concerns sulfadiazine is that of Maisel, McSwain and Glenn,[8] who studied tissue reactions in the dog. They found degenerative alterations in the "germinal centers" of the Malpighian bodies in nearly all of their animals. Davis, Harris and Schmeisser[4] observed focal necrosis, polymorph infiltration and nuclear fragmentation in the spleens of rats given sulfanilamide. Rake, Van Dyke and Corwin[9] described disorganization and disappearance of the Malpighian bodies in mice given 1% and 2% sulfathiazole diets. Lederer and Rosenblatt[7] saw similar changes in the spleen and lymph nodes of 4 human cases, who died after sulfathiazole treatment.

The changes described in Cases 1 and 2 were quite similar to those quoted above: the spleen displayed focal fibrinoid necrosis of the lymphoid elements in the Malpighian bodies. Nuclear fragmentation and cellular débris were marked and neutrophilic infiltration occurred throughout and in the margins of the necrotic foci.

The mesenteric lymph nodes showed similar focal, sometimes diffuse necrosis, which affected the cortical nodules particularly. The lymphocytes were decreased or absent in such areas and nuclear pyknosis and fragmentation were outstanding. This localization to mesenteric lymph nodes would seem, at first, to indicate an effect secondary to intestinal absorption of the sulfadiazine. However, the submucosal lymph follicles of the small intestine were unaffected.

Case 3 served as a control: there were no alterations in the lymph nodes except hyperemia and scattered hemorrhages but only the peribronchial nodes were available for examination. The spleen of this

patient presented changes characteristic of acute splenic tumor. This was very different from the picture in the other 2 cases.

Bone Marrow. Among the toxic effects of sulfadiazine upon the blood-forming organs, the depressing action on erythrocyte and granulocyte production assumes major importance. Such effects were described experimentally and clinically (Maisel, McSwain and Glenn,[8] Curry,[3] Satterthwaite[10] and Boyer.[1] Peripheral blood counts and bone marrow examinations revealed no comparable toxic action in the cases presented in this report.

Stimulation of megakaryocytes was apparent in the bone marrow of all 3 patients. No platelet counts were performed and the only significant clinical correlation was with the petechial and purpuric skin eruption in Cases 1 and 2. Whitehouse and Watkins,[11] and Gorham, Propp, Schwind and Climenko[6] described thrombocytopenic purpura following the use of sulfadiazine. Such reports indicate, therefore, that selective depressing effects may occur in susceptible individuals.

The possible relation of the splenic changes described above to the megakaryocyte activity is interesting, particularly since the spleen plays some rôle in thrombocytopenic purpura. No additional information is advanced in this report, however, and the findings in the spleen and bone marrow may be entirely independent.

Summary. 1. Three fatal cases of streptococcic infection are presented with complete autopsy findings. All of them received sulfadiazine treatment.

2. In 2 patients who developed a drug eruption, severe fatty metamorphosis of the liver and moderate focal fibrinoid necrosis of the spleen and mesenteric lymph nodes were observed. The 3rd patient showed no skin eruption, no necrosis of spleen or lymph nodes, and only mild fatty alterations were encountered in the liver.

3. A skin eruption during sulfadiazine treatment is of serious significance. *If a decision to continue with the drug is made following its appearance, then toxic effects should be expected and weighed against any possible beneficial influence on the original infection.*

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CARCINOMA OF THE NASOPHARYNX

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Periodically there arises in the literature a review of this subject, but inquiry among recent medical graduates and others contacted in a large urban hospital reveals the general unawareness of carcinoma of the nasopharynx and its clinical syndrome. This lack of knowledge has undoubtedly been a factor in the poor control of this highly malignant disease. Every review in the literature presents an equally discouraging percentage of "cure." Many authors stress the element of late diagnosis as one of the reasons for this low percentage. Hence it seems desirable that various clinics should report their cases and the factors behind the therapeutic failures. We are reporting on 17 cases occurring at this hospital, 10 of which we have studied personally.

Martin and Blady[5] report that carcinoma of the nasopharynx comprises 2% of the malignant growths seen in the Head and Neck Clinic of the Memorial Hospital in New York. They also point out that this tumor occurs in a younger age group (mean age 45 years) than do tumors of the tongue, lip and mouth (56 to 58 years). It is interesting to note that several Chinese are included in many of the large series; Lenz[4] has 4 in a series of 63. Various authors report slightly different incidences of the following features:

1. *Cervical Adenopathy.* Kasaback[3] in 57 cases reports 77% showing cervical metastases on admission. Lenz[4] lists 36% in 61 cases. Furstenburg[1] states that 27.5% of his 41 cases showed cervical adenopathy on admission, but by the time the diagnosis was made 60% had palpable nodes in the neck.

2. *Nasorespiratory Symptoms.* Roughly 30% of cases in the literature give as a first symptom nasal obstruction, discharge or epistaxis.

3. *Neurologic Symptoms.* New[7] reports in 194 cases that 31% had paralysis of one or more cranial nerves. Other authors since have reported essentially similar figures. The most frequently involved cranial nerves are V, VI and IX, resulting in facial pain, diplopia and dysphagia respectively. These findings, plus headache, are explained by direct extension of the tumor into the middle fossa of the skull. Roentgenograms of the base of the skull show a typical melted-out appearance of the sphenoid and the petrous portion of the temporal bone. There are those[5] who claim that these findings are due to the erosive properties of the tumor once in the skull rather than by direct extension through the bone. They point out a possible pathway along the cartilaginous portion of the Eustachian tube up through the foramen lacerum accompanying the internal carotid artery (Fig. 9). Frequently it spreads a considerable way beneath the dura eroding the

* Now in active service, M.C., U.S.N.R.

bone during its passage. Due to the involvement of the cervical sympathetic chain, a Horner syndrome may develop.

4. *Ear Symptoms.* As most of the tumors arise in or near the fossa of Rosenmuller, a number of auricular manifestations may be expected as early complaints. Martin and Blady[5] state that unilateral deafness was the first symptom in 10% of their cases. Tinnitus and a sensation of stuffiness are the other leading complaints. Later severe earache may be prominent.

5. *Duration of Symptoms.* Furstenburg[1] claims that the average duration of symptoms before diagnosis was 15 months. Precious time has been lost in the performance of many operations done on erroneous diagnoses. For example, tonsillectomies, mastoidectomies, and so forth were done in 32% of the cases of Hauser and Brownell.[2]

Treatment. Once the diagnosis is proven, irradiation to the limit of the skin and physical tolerance is the only accepted form of treatment.* Martin and Blady[5] describe an ingenious radon applicator for topical application to the primary tumor in the nasopharynx. New[7] states that patients who were adequately treated with irradiation live 5 times as long as those who were not treated at all. One of the common faults in the handling of this condition has been to start treatment before the diagnosis has been established by biopsy. The tumor is so radiosensitive that any little irradiation may obliterate tissue favorable for biopsy, and the diagnosis is only secondarily established by removal of recurrent metastatic cervical nodes. The general opinion is that surgery is not indicated in the treatment of these tumors.

Analysis of Material. The accompanying chart of our 17 original cases shows numerous features confirming findings previously reported. Thus a younger mean age (38.5 years) is demonstrated than, for example, in malignancy of the mouth (56 to 58 years). Of our cases, 15 are males while only 2 are females. Once again the interesting incidence of Chinese in these cases becomes apparent, for 2 of our patients are of this race. Four negroes and 11 whites comprise the remainder. On admission every case had cervical lymph node metastases. In 11 of these patients the cervical lymph node enlargement was the original complaint. Three individuals complained primarily of epistaxis; 10 others developed it eventually. One referred to the ear in his original symptomatology, but 13 showed tinnitus or deafness in the course of their disease. In comparison with Needles'[6] report of the occurrence of Horner's syndrome in 4 out of 35 cases, we had 1 in 17. Nine individuals showed signs of cranial nerve involvement. Roentgen rays of the base of the skull showed a melted-out defect of the middle fossa in 5 cases. In 2 cases there was clinical evidence of involvement of the cranial nerves without Roentgen ray evidence of damage to the base of the skull (Cases 9 and 17). The reverse was true in 1 case (Case 8). The average length of time from the onset of the first symptom to the time of diagnosis was 8.1 months. Of the

* Irradiation should be given to each side of the face and neck with the portals extending about 1 inch above the zygomatic level and down to the base of the neck—approximate size of the field, 10 by 20 cm. Total fractional doses should average 3000 r, in air to each skin area. (Factors: 200 kv., 0.5 mm. Cu and 1 mm. Al filtration; 20 ma.; HVL 0.95 mm. Cu.) Occasionally additional treatment may be necessary.

17 cases, only 2 are alive (Cases 14 and 17). In the other cases the average length of life following the first symptom was 23.4 months. This figure represents the life span of a group of individuals admitted with cervical node metastases who received varying amounts of irradiation. This study, therefore, is a discussion of patients with late carcinoma of the nasopharynx. As in most other series, we are not in a position to offer comments on the early carcinoma of this region or any figures on the natural course of the disease unaffected by irradiation.

Pathologic Anatomy. Considerable confusion has centered about the term "lympho-epithelioma" coined by Schmincke[8] in 1921. The clinical syndrome produced by these tumors and their great radiosensitivity have led many to think of these as members of the malignant lymphomata or as representing an entirely new type of tumor. Schmincke pointed out that these tumors arose in a "lympho-epithelial" region, where normally considerable lymphoid tissue abounds, and that they were simply anaplastic carcinomas arising from the nasopharyngeal mucosa with many lymphocytes mixed in coincidentally. This is the commonly held view today. That these tumors are carcinomas may be readily seen from the accompanying photomicrographs. The same illustrations show that not all of them would fit the Schmincke description of "lympho-epithelioma." The tumors in our series tend to fall into 3 groups:

Group I (4 cases). This tumor consists of multiple, small, sharply demarcated but closely approximated islands of loosely packed cells. The individual cells contain rather small oval nuclei with one or two large nucleoli and a fairly coarse network making the nucleus appear dark. Abundant cytoplasm keeps the nuclei well separated. An occasional lymphocyte is seen between the cell groups. This microscopic picture is seen in Cases, 1, 6, 11 and 16 (Figs. 1 and 2).

Group II (2 cases). The second variety is made up of small single cords of tumor cells widely separated by an abundant stroma containing many lymphocytes and plasma cells. These cords, under low power, are strongly suggestive of anaplastic squamous carcinoma. The individual cells in the cords vary greatly. Some contain small dark staining oval nuclei while others contain large pale staining nuclei with large nucleoli. Cytoplasm in both types of cells is abundant. No prickle cells are seen. Such a microscopic picture is shown by Cases 4 and 14 (Figs. 3 and 4).

Group III (10 cases). This group of tumors embraces the largest number of our cases. It, in turn, is broken down into 3 subtypes. The basis of the subdivision is on the appearance of the general pattern, the cells being essentially similar.

Subtype A (5 cases). The tumor assumes the form of large invading solid blocks of tissue studded with cells containing uniformly huge pale-staining nuclei. These nuclei have exceedingly large nucleoli and a very delicate linin network. The cytoplasm of each cell appears to be merged with that of the next creating a pseudohomogeneous background for the nuclei. Only a few lymphocytes are seen nestled within this "block" of tumor tissue. Cases 2, 5, 8, 13 and 17 fall into this group (Figs. 5 and 6).

TABLE 1.—DATA ON 17 ORIGINAL CASES OF PRIMARY CARCINOMA OF THE NASOPHARYNX

Patient	Age	Sex	Color	First symptom or sign (date)	Months before diagnosis was made	Cervical nodes	Nasal and ear symptoms	Cranial nerve or intracranial symptoms	Skull involvement by Roentgen ray	Length of life
1. R. M.	26	M	W	Epistaxis (Nov. 1923)	12	Yes	Epistaxis	...	None; metastases to lungs	Died July 22, 1926 (32 mos.)
2. C. S. L.*	56	M	Y	Cervical nodes (April 1923)	8	Yes	...	...	...	Died Feb. 12, 1924 (10 mos.)
3. O. O.	63	M	W	Nasal discharge and cervical nodes (Jan. 1926)	22	Yes	Epistaxis, deafness (June 1926)	...	...	Died June 29, 1928 (40 mos.)
4. M. S.	33	M	B	Cervical nodes (1927)	..	Yes	...	...	...	Died Apr. 12, 1928
5. C. N.	34	M	W	Cervical nodes (1936)	5	Yes	Deafness	VI, July 1937, headache	Yes	Died Oct. 27, 1938 (23 mos.)
6. V. L.*	26	M	W	Cervical nodes (Sept. 1938)	5	Yes	Deafness	Headache	None	Died Nov. 17, 1939 (15 mos.)
7. O. L.*	52	M	W	Cervical nodes (1935)	6	Yes	Deafness	VI, headache	...	Died Aug. 25, 1939 (48 mos.)
8. S. C.	35	F	W	Cervical nodes (July 1939)	13	Yes	Tinnitus	III, V, VI, VII (R), VI (L), Horner's syndrome	None	Died May 22, 1942 (34 mos.)
9. W. P.*	19	M	B	Tinnitus (Jan. 1940)	2	Yes	Epistaxis and tinnitus	...	...	Died June 25, 1942 (30 mos.)
10. R. A.	15	F	B	Cervical nodes (1940)	11	Yes	Epistaxis, deafness (L)	VI, IX and X	Yes	Died Jan. 1943 (36 mos.)
11. D. L.*	19	M	W	Cervical nodes (Feb. 1940)	1	Yes	...	IX	...	Died Feb. 22, 1941 (12 mos.)
12. M. A.*	59	M	W	Epistaxis (Dec. 1941)	7	Yes	Epistaxis, tinnitus and deafness	IX	Yes	Died Feb. 22, 1941 (13 mos.)
13. V. F.*	18	M	B	Cervical nodes (Dec. 1941)	8	Yes	Deafness, epistaxis and tinnitus	III, V, VI, IX	Yes	Died Mar. 31, 1943 (17 mos.)
14. A. Y.	71	M	W	Epistaxis (May 1942)	6	Yes	Deafness, epistaxis and tinnitus	Headache and ataxia	Yes	Still alive and in good health
15. L. C.*	47	M	Y	Cervical nodes (April 1942)	10	Yes	Epistaxis and tinnitus	...	...	Died Feb. 25, 1943 (10 mos.)
16. C. C.	45	M	W	Pain in back (Oct. 10, 1942)	4	Yes	Nasal obstruction and epistaxis	Deafness	Metastases to spine	Died May 7, 1943 (8 mos.)
17. C. V.	33	M	W	Cervical nodes (June 1942)	9	Yes	Epistaxis and nasal obstruction	VI	None	Still alive and in good health

*=Autopsy.

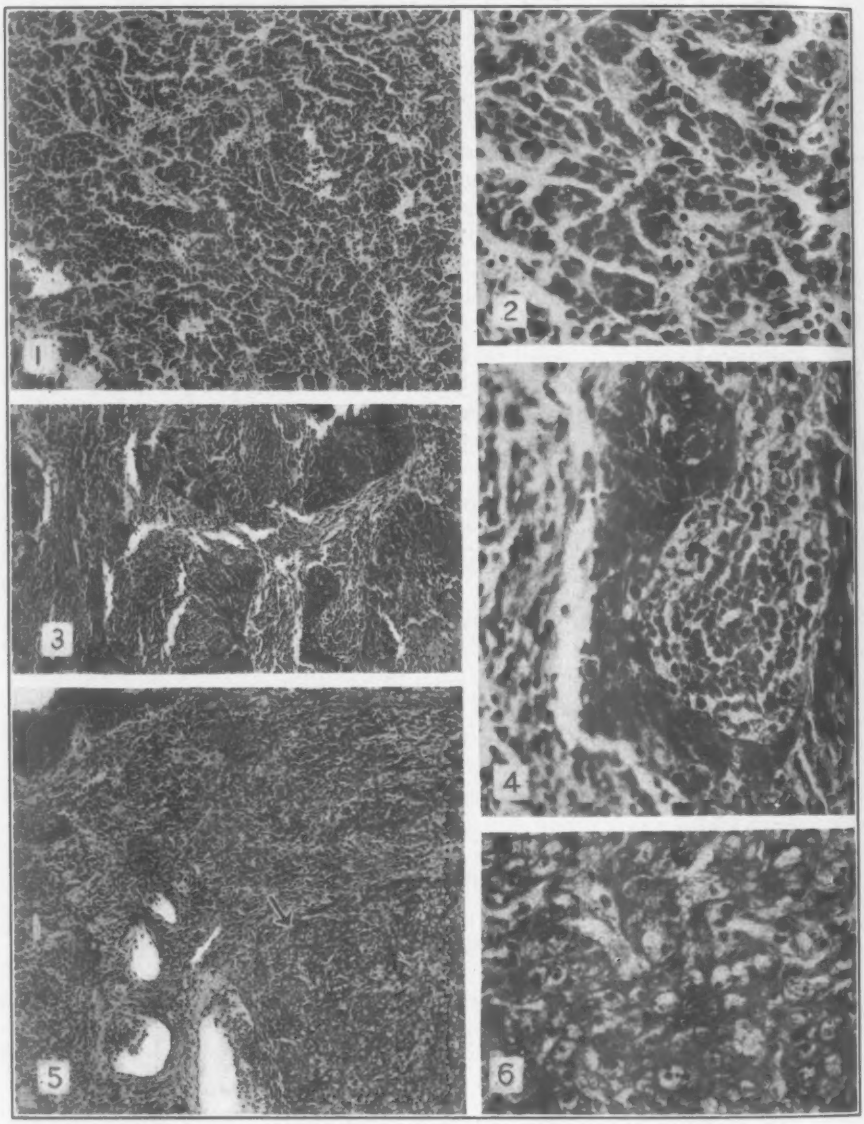

FIG. 1.—Carcinoma of nasopharynx, Group I, as described in text. (Hematoxylin and eosin, × 80.)

FIG. 2.—Same as Figure 1 (× 322).

FIG. 3.—Carcinoma of the nasopharynx, Group II, as described in text. (H and E stain, × 80.)

FIG. 4.—Same as Figure 3 (× 322).

FIG. 5.—Carcinoma of nasopharynx, Group III, Subtype A, as described in the text. (H and E stain, × 80.) The arrows outlined the tumor margin.

FIG. 6.—Same as Figure 5 (× 322).

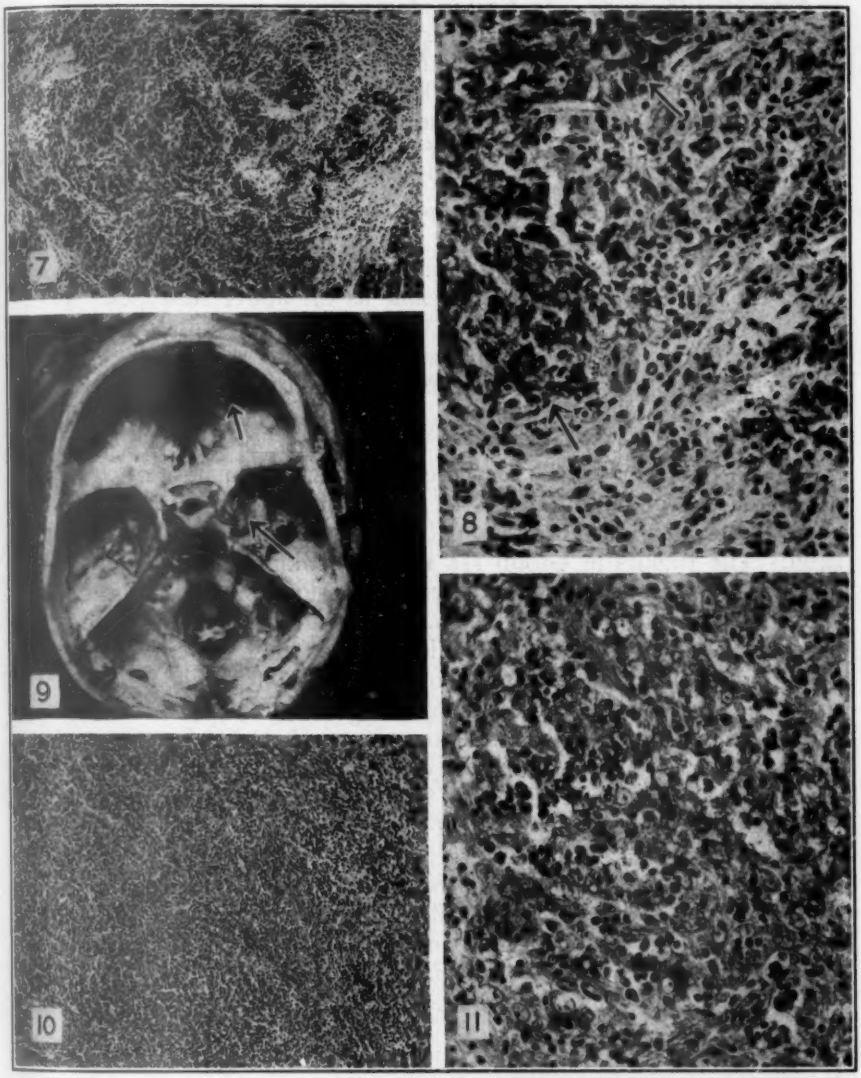

FIG. 7.—Carcinoma of nasopharynx, Group III, Subtype B, as described in the text. (H and E stain, × 80.)

FIG. 8.—Same as Figure 7 (× 322). The arrows point to the tumor margin.

FIG. 9.—Case 13, illustrating the path of extension of these tumors up along the internal carotid artery. The posterior arrow points to tumor. The anterior arrow points to tumor nodules in the roof of the right orbit. Subsequent dissection showed the orbit to be filled with tumor which was continuous through the orbital fissure with the portion shown by the posterior arrow. The reason for the frequent involvement of the III, IV, V, VI cranial nerves becomes obvious from this illustration. The right Gasserian ganglion has been forced posteriorly by the tumor.

FIG. 10.—Carcinoma of the nasopharynx, Group III, Subtype C, as described in the text. (H and E stain, × 80.)

FIG. 11.—Same as Figure 10 (× 322).

Subtype B (3 cases). Instead of showing large blocks of tissue, this tumor features poorly organized, irregular nests and cords of tumor cells creeping out into the nearby stroma. The nuclei of the cells here are of the same general nature. They are considerably smaller than those of Subtype A but are pale-staining with large nucleoli and delicate linin network. In this tumor there is a generous sprinkling of lymphocytes in between the tumor cells in contrast to their relative absence in Subtype A. Cases 7, 9 and 12 are of this type (Figs. 7 and 8).

Subtype C (2 cases). This type represents the least organization. Very thin cords of cells weave an entirely irregular pattern. Once again the cells are essentially the same as the above subtypes. The prominent nuclei in the thin cords of cells create the appearance of a diffuse scattering of cells throughout the stroma. Many lymphocytes are seen generally in amongst the tumor cells. Cases 3 and 10 show this structure (Figs. 10 and 11). No doubt, it is Subtype B and C which Schmincke referred to as "lympho-epitheliomas."

The postmortem studies of these cases reveals an interesting tendency for the tumor in Group I to metastasize widely to lungs, liver, and so forth, in addition to local extension into the middle fossa of the skull. The tumors in Group III show a striking tendency to local metastasis to cervical nodes and direct extension up along the internal carotid artery into the middle fossa. The latter cases have not shown general metastases. There is no evidence that these cases have shown symptoms earlier, and that as a consequence came under irradiation therapy earlier. Further study along this line should prove informative.

Comment. It should be pointed out that profoundly ill patients can be dramatically relieved temporarily by irradiation. In several of our recent cases patients were rendered symptom-free for weeks or months with complete clinical regression of the primary and also the cervical node enlargement. Subsequent recurrence of the tumor or the metastases has been found to be radioresistant; therefore, once the diagnosis has been established, all patients should be treated to the limit of the skin and physical tolerance even though clinically one can no longer find disease. The practice of irradiating cervical lymph node enlargement without adequate examination of the nasopharynx is to be condemned.

Summary. A series of 17 original proven cases of carcinoma of the nasopharynx has been presented with their clinical and pathologic characteristics. The lack of general cognizance of this tumor and therefore its late diagnosis has been emphasized. The clinical syndrome as presented above represents late disease. The radiosensitivity of these tumors leads to marked temporary improvement, hence it is of value even in very advanced cases.

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"DRUG FEVER" ACCOMPANYING SECOND COURSES OF SULFATHIAZOLE, SULFADIAZINE AND SULFAPYRIDINE

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The phenomenon of fever occurring as a result of therapy with sulfanilamide was first described by Hageman and Blake,[2] and has since been commonly observed by all clinicians making extensive use of any of the sulfonamide drugs. Such "drug fevers" often appear around the 7th to the 10th day of treatment with a sulfonamide drug, although they may occur at any time after treatment is begun. They are frequently accompanied by dermatitis with or without conjunctivitis. Lyons and Balberor[3] reported that 19 (36%) of 53 patients who received a second course of sulfathiazole experienced fever after failing to develop fever during a first course, whereas the percentage of patients who developed fever during a first course of sulfathiazole which lasted for 7 days or longer was 10.4%.

Several questions occurred to us with regard to the application of these findings: First, will drug fever occur as frequently following two courses of the other sulfonamides as it does following two courses of sulfathiazole? Second, is a second course of a different sulfonamide as likely to cause fever as a second course of the same drug? Third, is this phenomenon related to the length of the first course, to the length of the interval between courses, or to the length of the second course of sulfonamide administration? Further, if a patient does not develop fever from two courses of a sulfonamide is he likely to develop it following later courses? In an attempt to answer these questions, we have analyzed the data on all the patients coming under our observation who have received more than one course of the sulfonamide drugs and who did not develop fever during the first course.

Results. As shown in Table 1, among 53 patients who received a second course of sulfathiazole, fever developed during this course in 9 (16.7%). When sulfadiazine* was given to 68 patients following an earlier course of the same drug 5 (7.4%) developed fever during the second course. Only 22 patients in our series received a second course of sulfapyridine. Two of these (9.1%) developed "drug fever." When the 144 patients receiving a second course of any of these 3 sulfonamides after an initial course of the same drug are considered as a single group, it will be seen that 16 (11.1%) experienced fever during the second course.

The second column, of Table 1 shows those patients who received a course of one of the sulfonamide drugs following an initial course of some

* Sulfadiazine for this study was supplied by the Lederle Laboratories, Inc.

other sulfonamide. In some instances an interval elapsed between the two courses, and in others the second sulfonamide was given immediately following cessation of administration of the first. Since there was no discernible difference between the proportion of patients developing fever after an interval had elapsed and those in whom the two drugs were given one after the other, we have included them all in the one group. Eighty-nine patients were given sulfathiazole after a previous course of another sulfonamide had not resulted in the production of fever. Five of these patients (5.6%) developed drug fever. One of the 57 patients receiving sulfadiazine and none of the 23 patients receiving sulfapyridine following the administration of a different sulfonamide developed drug fever. When this group is totaled, it is seen that among 169 patients receiving a second sulfonamide after the first failed to produce fever, 6 patients (3.6%) developed drug fever.

TABLE 1.—PATIENTS DEVELOPING FEVER DURING VARIOUS TYPES OF SULFONAMIDE ADMINISTRATION

Previous course of	Same sulfonamide	Another sulfonamide	No previous sulfonamide
Sulfathiazole:			
All cases	53	89	172
Febrile cases	9	5	14
% febrile	16.7	5.6	8.1
Sulfadiazine:			
All cases	68	57	371
Febrile cases	5	1	16
% febrile	7.4	1.8	4.3
Sulfapyridine:			
All cases	22	23	194
Febrile cases	2	0	7
% febrile	9.1	0	3.6
All 3 sulfonamides:			
All cases	144	169	737
Febrile cases	16	6	37
% febrile	11.1	3.6	5

The two groups described above may be compared with those who were observed while receiving their first course of a sulfonamide. Only patients who received the drugs for 6 days or longer, are included in these figures. Sulfathiazole was given to 172 patients among whom 14 (8.1%) developed fever. Sixteen (4.3%) of the 371 patients receiving sulfadiazine experienced fever, as did 7 (3.6%) of the 194 to whom sulfapyridine was administered.

When these results were tested by the chi square method, the figures in the last line where patients treated with the 3 sulfonamides are computed together, are statistically significant. The proportion of patients developing fever upon receiving sulfathiazole after a first course of sulfathiazole is significantly greater than the proportion in patients receiving sulfadiazine following a first course of sulfadiazine. Likewise the proportion of patients developing fever upon receiving sulfathiazole following sulfathiazole is significantly greater than that in patients receiving sulfathiazole following another drug, but the difference between those receiving sulfathiazole following sulfathiazole compared to those receiving a first course of sulfathiazole does not

quite fill the criteria for statistical significance (one-half p is slightly over 3% whereas it should be 2.5% or less to be considered significant).

It will be noted, however, that even in the instance of those individual drugs (sulfadiazine and sulfapyridine) where the number of cases is not sufficient for the figures to be significant, the trend is in the same direction as the results obtained with the use of sulfathiazole. Furthermore, as has been noted above, the figures for the totals on all 3 drugs are significant.

Patients Receiving More Than Two Courses. Three courses of a sulfonamide were administered as follows: sulfathiazole, 3 patients; sulfadiazine, 2 patients; sulfapyridine, 1 patient. Four courses of sulfathiazole were given to 1 patient and four courses of sulfadiazine to 4 patients. One patient was given six courses of sulfadiazine. None of these patients had a febrile reaction attributable to sulfonamides at any time. The longest period covered from the beginning of the first course to the end of the last was 596 days, during which four courses of sulfadiazine were given, separated by three intervals during which no sulfonamides were administered.

Influence of Length of Courses or of the Interval Between. In the patients who received two courses of the same sulfonamide, the length of the first course varied from 1 to 35 days (mean 7.1 days) in the sulfathiazole-treated patients; from 1 to 64 days (mean 10.7 days) in the sulfadiazine-treated patients, and from 1 to 31 days (mean 6.8 days) in the patients to whom sulfapyridine was administered. We were unable to find any relationship between the length of the first course and the development of fever during the second course. The length of the interval between courses varied from 1 day to 27 months in the case of sulfathiazole, between 1 day and 19 months in the sulfadiazine-treated patients and between 1 day and 22 months in the sulfapyridine-treated patients. As will be seen from Table 2, febrile reactions occurred after varying intervals, the shortest period of time elapsing between courses being 1 day and the longest 7 months and 6 days. Febrile reactions were no more frequent when the interval was short than when it was long and *vice versa.*

The length of the second course of sulfathiazole varied from 1 to 17 days; of sulfadiazine from 1 to 79 days, and, in the case of sulfapyridine, from 1 to 12 days. Again, we were unable to find any relationship between the length of the second course and the incidence of drug fever. When a febrile reaction did supervene, it began anywhere from the 1st to the 7th day of the second course of the drug. When the total length of time covered by the first course of the sulfonamide, plus the interval, plus the second course was considered, it bore no relation to the number of febrile reactions.

Table 2 also shows that a drug rash was present in addition to the febrile reactions in 6 of the 9 patients with fever following a second course of sulfathiazole; in 3 of the 5 patients with fever following a second course of sulfadiazine and in both of the patients experiencing fever following a second course of sulfapyridine. Conjunctivitis was present in addition to dermatitis in 1 patient each receiving sulfathiazole and sulfadiazine.

TABLE 2.—PATIENTS WITH FEBRILE REACTION TO SECOND COURSE OF SULFONAMIDES

Case No.	Duration of first course (days)	Interval between courses (days)	Day of second course when fever began	Dermatitis or conjunctivitis
Sulfathiazole Following Sulfathiazole				
1	6	2	5	No
2	20	3	1	D
3	7	14	4	D
4	1	3	7	D
5	2	8	3	D
6	1	28	2	No
7	8	24	2	No
8	4	4	2	D and C
9	4	21	5	D
Sulfadiazine Following Sulfadiazine				
10	10	6	5	D
11	21	7 mos. and 6 days	1	No
12	13	6	1	D
13	4	1	1	D and C
14	20	6	1	No
Sulfapyridine Following Sulfapyridine				
15	9	2	10	D
16	20	5	2	D

Discussion. We have been able to confirm the findings of Lyons and Balberor[3] that fever follows the administration of a second course of sulfathiazole more frequently than it occurs during a single course and to show that this result is also obtained after therapy with other sulfonamides, that is, sulfadiazine and sulfapyridine. While the percentage of febrile reactions in our series following a second course of sulfathiazole (17.1%) was not as high as that found by Lyons and Balberor[3] (36%), this may have been due to a difference in the dosages used in the second course. The former authors gave 4 gm. of sulfathiazole followed by 1 gm. every 4 hours. In approximately one-half of our cases this dose was given, while in the others, a dose of 2 gm. initially and 0.5 gm. every 4 hours was used. Febrile reactions tended to occur more frequently in the patients who received the higher doses.

Fink and Wilson[1] found that among 86 children given sulfathiazole, 3 developed febrile reactions; and that among 91 who received sulfadiazine, 4 experienced febrile reactions. It is possible that the fact that the subjects used in this investigation were all children may have accounted for the low incidence of drug fever, since it has been the experience of many observers that reactions from the sulfonamides in general are less frequent in children than in adults. Unfortunately, the authors did not state for comparison the number of febrile reactions which occurred in children under their observation receiving only one course of the sulfonamides. On the other hand, the low incidence of febrile reactions may have been due to the use of low dosages necessitated by the fact that the subjects were children.

If a second course of a sulfonamide is given to an adult after an interval of time has elapsed since the administration of a course of the same sulfonamide, a febrile reaction is likely to occur, especially if a full dose of the drugs is used. On the other hand, as the second line

of Table 1 shows, if another sulfonamide is given for the second course, instead of the same sulfonamide, febrile reactions are not any more frequent than during a single course of a sulfonamide and may possibly occur less often. The practical application of this is obvious; if a second course of a sulfonamide is needed and another drug is available which is as potent as the first one, the second drug should be used for the succeeding course. Apparently, the length of time covered by the first or second courses or of the interval between has no effect upon the tendency for febrile reactions to develop, except that none of the febrile reactions developed earlier than the 10th day following the commencement of the first course of the drug, with the exception of 1 case in which the fever began after 4 days of sulfadiazine therapy, a 1-day interval during which no drug was given and less than 1 day of subsequent sulfadiazine administration. By contrast, none of the patients who received a different sulfonamide during the second course developed a febrile reaction earlier than the 3rd day of administration of the second sulfonamide.

Since none of our 12 patients who were given from 3 to 6 courses of a sulfonamide developed febrile reactions during any course, it is possible that patients who are going to develop drug fever will do so during the first or second course or not at all. A larger group of patients who have received multiple courses will be needed to prove this point, however.

Summary and Conclusions. 1. Among 144 patients who received a second course of sulfathiazole, sulfadiazine or sulfapyridine after a varying interval of time had intervened since the first course of the same sulfonamide, 16 (11.1%) developed drug fever. Eleven of these patients developed concomitant dermatitis, which in 2 instances was associated with conjunctivitis.

2. Among 169 patients who received a second course of sulfathiazole, sulfadiazine or sulfapyridine following a first course of another sulfonamide, 6 (3.6%) developed drug fever.

3. Among 737 patients who were observed during a single course of therapy with sulfathiazole, sulfadiazine or sulfapyridine, 37 (5%) developed febrile reactions.

4. Febrile reactions were more frequent following a second course of sulfathiazole as well as during a single course of sulfathiazole than was the case with sulfadiazine or sulfapyridine.

5. Three to 6 courses of the same sulfonamide were given to 12 patients, none of whom developed febrile reactions.

6. It is concluded that, when a second course of a sulfonamide must be given to a patient, regardless of the interval following the first course, another sulfonamide drug should be given.

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INSULIN RESISTANCE

THE RÔLE OF IMMUNITY IN ITS PRODUCTION

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IT is well known that insulin is a poor antibody producer. Barral and Roux,[3] Lewis[18] and Bernstein, Kirsner and Turner[5] were able to demonstrate sensitization of guinea pigs by means of the Schultz-Dale technique or by anaphylactic reactions. More recently Wasserman, Broh-Kahn and Mirsky[25] have demonstrated antibodies in rabbits injected with insulin by means of the complement-fixation technique. Other investigators have failed to produce antibodies to insulin. In my own experiments rabbits and guinea pigs receiving insulin subcutaneously and intraperitoneally failed to develop skin hypersensitivity or circulating antibodies as measured by the precipitin test, nor did their serum protect a normal animal against a minimal lethal dose of insulin.

The fact that insulin is a poor antigen is rather fortunate for diabetics. Many diabetic patients receiving insulin for the first time develop local reactions. Such reactions usually disappear after a few injections, although they may persist for a long time in an occasional case. In either event such patients respond to insulin in the usual fashion

Some patients become hypersensitive to insulin, developing generalized as well as local reactions. Some of these patients have been reported to have positive skin tests to more than one type of insulin,[2,4,6,9,10,24] passive-transfer antibodies,[7,22,24] and precipitins.[24] They may or may not respond to insulin in the usual fashion. Only an occasional patient becomes resistant or refractory and requires tremendous doses to control the diabetes. Several such patients have been reported and in a few instances immunologic studies have been made. The patient described by Glassberg, Somogyi and Taussig[12] developed local and urticarial reactions first, and later, insulin resistance, with disappearance of skin reactions. This patient's serum did not contain precipitins. The cases of insulin resistance reported by Wiener,[28] Martin, Martin, Lyster and Strouse[21] and Glass, Spingarn and Pollack[11] showed no passive-transfer or other types of antibodies. On the other hand, the patient of Karr, Kreidler, Scull and Petty[15] showed positive skin tests to all types of insulin, passive-transfer antibodies and precipitins for insulin. All of these reports agree that the patients' serum does not antagonize the hypoglycemic effect of insulin in animals. On the other hand, Cannon and co-workers,[8] Lowell,[19] and the author[16] have obtained evidence of the opposite sort, which will be discussed more fully below. It is true that Glen and Eaton[13] and Wayburn and Beckh[27] have also demonstrated an insulin-antagonizing effect of the serum from such patients,

but they attributed it to an anterior pituitary diabetogenic factor. Similarly Marble, Fernald and Smith[20] were inclined to attribute the delayed anti-insulin effect of the serum from 2 insulin-resistant patients to the action of a pituitary factor.

Material and Method. The blood from 6 patients with insulin resistance was examined for the presence of insulin antibodies. The ring precipitin method and the Praussnitz-Kustner test were largely employed. In performing the precipitin test the antiserum was absorbed with bovine and pig serum previous to testing, and dilutions of the antigen, starting with 0.5 or 1% solution of crystalline zinc insulin,* were layered over the sera. In some instances amorphous insulin from different sources was substituted, without affecting the results. In the Praussnitz-Kustner test, 2 units of crystalline zinc insulin were used to test for the presence of passive-transfer antibodies. In addition the sera from several patients suspected of being resistant to insulin, and from patients showing transient or persistent local reactions to insulin were examined by these methods. In some instances the attempt was made to determine if the sera from resistant cases would protect guinea pigs against a lethal dose of insulin. In 1 case, studied more extensively than the others, the "insulin tolerance test" was determined and compared with such a test in the usual diabetic case.

TABLE 1.—IMMUNE REACTIONS OF SERUM FROM INSULIN-RESISTANT PATIENTS AND THEIR INSULIN REQUIREMENT

Case No.	Antiserum incubated with bovine and pig serum	Dilutions of crystalline zinc insulin 0.5%							Passive transfer test	Daily insulin dosage (units)	
		1	4	16	64	256	1000	10,000			
1	E.St.C. (a)	+++	+++	++	++	++	+	±	+++	450	1/9/41
	E.St.C. (b)	++	+	±	−	−	−	−	+++	100	2/25/42
	E.St.C. (c)	++	++	++	+	±	−	−	+++	200	3/21/43
2	Fr.P.	−	−	−	−	−			Neg.	50	Neg. precip. test with dilutions of 1% insulin
3	A.LeV.	−	−	−	−	−			Neg.	63	"
4	E.P. (a)	+	+	±	−	−			++	200	
	E.P. (b)	−	−	−	−	−			Neg.	46	"
5	H.T.	−	−	−	−	−			+	160	"
6	A.M.	−	−	−	−	−			+++	200+	"

Heating serum for 1 hour at 56° C. did not affect the results.

Results. The results of the precipitin tests are summarized in Table 1. This table deals only with data obtained on 6 patients who showed evidence of insulin resistance. The sera from several normals and from several diabetic patients were tested, including the sera from 2 patients in whom insulin injections caused persistent local reactions. They all failed to show circulating antibodies to insulin or passive-transfer antibodies. The sera from some of the patients receiving insulin did show a small titer of antibodies to bovine or pig serum (1:2 to 1:10 dilution of antigen).

CASE 1.—This patient, E. St. C., came under observation at this hospital in October, 1940. She had had rheumatoid arthritis for 13 years and diabetes for 6 years. She had been treated from the beginning of her diabetes by members of the Joslin Clinic. They discovered that about 2 months after the beginning of insulin treatment her requirement for insulin rose to 400 to

* I am indebted to Dr. F. B. Peck of Eli Lilly & Company for a supply of crystalline zinc insulin.

500 units daily. At times as much as 700 units daily were used in an attempt to control the glycosuria; she was resistant to any type of insulin, including crystalline insulin. In addition she had severe local reactions, resulting in subcutaneous nodules of inflammation and necrosis at the sites of injection. During her 4-month stay at the Massachusetts General Hospital the dosage of insulin varied between 150 and 450 units daily. This resistant state was

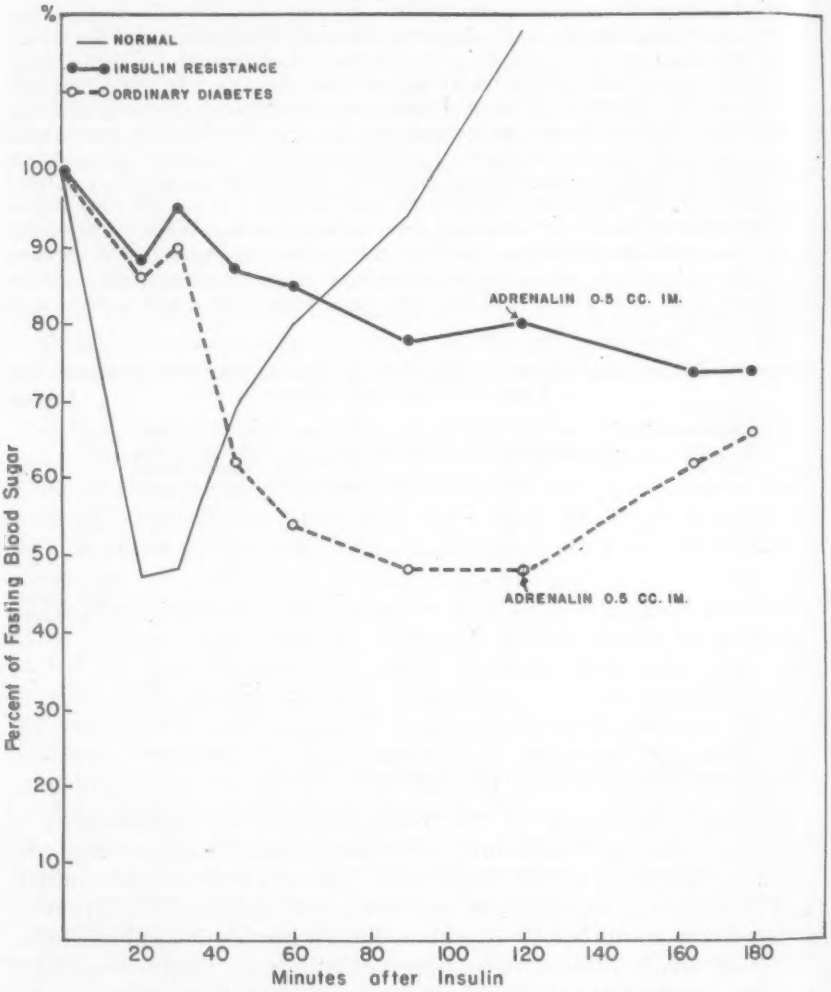

FIG. 1.—The insulin tolerance test of a patient with insulin resistance (E. St. C.) compared with that of a patient with ordinary diabetes. The "normal" insulin tolerance is charted for reference.

verified by the fact that 10 units of insulin intravenously failed to produce the expected drop in blood sugar. As shown graphically in Fig. 1, the blood sugar of the usual diabetic falls rapidly to 47% of the fasting level in 90 minutes. In other words, the ordinary diabetic is "insulin-sensitive." On the other hand, the blood sugar of this patient dropped very little, reaching 78% of the fasting level in 90 minutes.

The serum of this patient contained circulating antibodies to insulin to a dilution of antigen of 1:200,000 (Table 1) and also gave a positive Praussnitz-Kustner test. Several months previously, Dr. Paul Cannon[8] also had found agglutinins for insulin and passive-transfer antibodies in her serum.

For several months after she left the hospital the insulin requirement was 700 units daily, but by February 1942, when another blood sample was obtained, her requirement had dropped to 100 units daily. At this time the precipitin reaction was positive only up to a dilution of 1:800. The serum still gave a positive Praussnitz-Kustner test up to a dilution of serum of 1:90. At the present, the precipitin test is positive up to a dilution of 1:12,000, the passive-transfer test is positive up to 1:90, and the insulin requirement is 200 units daily.

An attempt was made to determine the physiologic activity of this serum. Theoretically such a serum should protect an animal against a lethal dose of insulin; or, if injected into an animal without insulin, it should cause a rise in blood sugar by antagonizing the animal's own insulin. The results of such experiments with this serum were equivocal, due, perhaps, to inadequate amounts of serum used.

The results in 5 other cases are recorded in Table 1. The serum of 2 patients (Fr. P. and A. LeV.) was made available through the kindness of Drs. Root and Marble. Both of these patients had gone through a period of insulin refractoriness for about a year. Their requirements ranged up to 2200 units daily, which they received without interruption. Unfortunately their serum was not examined during this phase for precipitins or passive-transfer antibodies; but Marble, Fernald and Smith[20] did find on 1 occasion an anti-insulin substance in the serum, which had a delayed effect. Later, when the requirement for insulin had returned to a level nearer normal (50 to 60 units daily), their serum contained neither circulating antibodies to insulin, nor passive-transfer antibodies.

The 4th patient (E. P.) was first seen on the wards of the Massachusetts General Hospital where his insulin requirement fluctuated between 100 to 140 units. At this time circulating antibodies against insulin were not demonstrable in the blood and it was felt that the high requirement for insulin was due to infection. However, 3 months later, when his requirement for insulin rose to 200 units daily, a blood sample obtained for us by Dr. Root gave a positive precipitin test up to a dilution of 1:800, and a moderately positive passive-transfer test. In addition 1 cc. of serum injected into each of 2 guinea pigs delayed the effect of a lethal dose of insulin in one, and neutralized it completely in the other. At present (a year later), his blood contains neither precipitins nor passive-transfer antibodies, and his insulin requirement is down to 46 units daily.

The serum of the 5th case (H. T.) was obtained from a patient of Dr. D. Hurwitz. No precipitins were found in this serum but a slight concentration of passive-transfer antibodies was demonstrable. The insulin requirement of this patient was only 160 units, indicating a rather mild degree of insulin resistance. Several months later the insulin requirement dropped to 60 units, but blood was not available for study.

The last patient (A. M.) displayed both insulin resistance and insulin sensitivity, and has been reported on by Dr. F. C. Lowell,[19] who was

kind enough to send us blood specimens for study. Intravenous insulin had no effect upon the blood sugar of this patient. Samples of blood taken during the administration of insulin and 1 month after its omission failed to show precipitins or agglutinins. One cc. of serum injected intravenously into a rabbit had no effect upon the blood sugar level of the rabbit over a period of 4 hours. On the other hand, the Praussnitz-Kustner test was strongly positive, the reaction lasting over 1 hour. Moreover, 1 cc. of serum injected intraperitoneally into each of 3 guinea pigs either prevented or delayed the hypoglycemia produced by 0.2 mg. of crystalline zinc insulin. These experiments along with those in Case 4, although few in number, confirm the antihormonic effect of such serum.

Discussion. The clinical fact that insulin, administered subcutaneously or intravenously, fails to affect the blood sugar in an insulin-resistant diabetic, in the presence of various types of antibodies to insulin, suggests immediately that the antibodies to insulin are the cause of the resistant state. These antibodies, either circulating or fixed, are able to neutralize injected insulin so that the requirement for insulin to control the diabetes is considerably increased. In other words, antibodies to insulin are antihormonic. The demonstration of substances in the serum of such a patient, which protect animals against the hypoglycemic effects of insulin, is strongly confirmatory of this viewpoint. Various types of antibodies are present, but not all types are demonstrable in any given case. For example, the serum of Case 1 failed to show biologic antagonism against insulin in spite of a high concentration of precipitins and passive-transfer antibodies, whereas the serum of Case 6 contained no precipitins but antagonized the action of insulin and gave a strong Praussnitz-Kustner test.

The data obtained in Case 1 strongly suggest that the degree of insulin resistance parallels the concentration of antibodies. This is also suggested by the results in Case 4. Here the precipitin and passive-transfer tests turned positive under observation as the degree of insulin resistance increased, and later became negative again as the insulin requirement dropped. In addition, Case 5 showed a negative precipitin test and only a mild passive-transfer test in the presence of a mild degree of insulin resistance.

The data in Cases 2, 3 and 4 suggest that the return of normal insulin sensitivity is dependent upon the disappearance of immune bodies. Similar fluctuations in antibodies have been observed in humans, such as the appearance of antibodies to cow's milk protein, egg white and other proteins when infants are first exposed to these foods and the subsequent disappearance of the antibodies, in spite of continued ingestion of such foods.[1] Likewise, I have observed the disappearance of antibodies to thyroglobulin in rabbits repeatedly injected with thyroglobulin. It would seem that repeated injections of insulin, rather than omission of insulin, offers a mode of therapy in bringing about desensitization and cure of insulin resistance. Theoretically, the worst thing one could do in such cases is to give insulin

at infrequent intervals. Such a procedure should enhance rather than diminish antibody production.

It has been reported by various investigators and confirmed by the results reported above, that the serum of insulin-resistant patients reacts almost alike with insulins from different animal sources, in spite of the fact that the resistant state may have been induced by a variety of insulin preparations. Moreover, such patients respond as poorly to one type of insulin as to another, including protamine insulin and crystalline zinc insulin. In other words, antibodies to insulin, in common with antibodies to other hormones, are hormone-specific rather than species-specific? In the case of antibodies to thyroglobulin, hormone specificity has been described by Hektoen and Schulhof[14] and by myself;[17] in the case of antibodies to the anterior pituitary this type of specificity has been described by various investigators.[23] Experimentally, the immunologic identity of insulins from various species has been shown by Lewis,[18] who used the Schultz-Dale technique, and by Wasserman and Mirsky,[26] who used the complement-fixation reaction.

It must be emphasized that hormone-specificity is only relative. The reaction of the antiserum may be greater with the hormones derived from some species than with those derived from others. It is weakest with the hormone derived from the donor species. For example, antiserum obtained by injecting rabbits with human thyroglobulin is 100 to 1000 times as potent when tested with human thyroglobulin as when tested with rabbit thyroglobulin. By analogy, the serum from insulin-resistant patients should antagonize human insulin much less than insulins derived from other species. This fact may explain some of the results reported by Lowell.[19] In his patient with insulin resistance, 30 units of human insulin caused a marked drop in blood sugar, whereas 30 units of crystalline insulin (animal) failed to do this. This is as expected on the basis of the analogy with thyroglobulin just mentioned. The comparison should be between 30 units of human insulin *versus* 3000 or more units of crystalline insulin (animal). Furthermore, his inability to demonstrate "protective antibodies" to human insulin in the presence of such antibodies to crystalline zinc insulin is also as expected. Any biologic protection test is undoubtedly too crude to detect slight amounts of antibodies to an antigen derived from the same species as the anti-serum is derived.

It is interesting to speculate as to what happens to the patients who survive the period of insulin resistance. At present, Patient 2 is controlled by 50 units of insulin daily, Patient 3 by 63 units, Patient 4 by 46 units, and Patient 5 by 60 units. The first patient is still resistant, and there are no further data on the sixth. The patient reported by Wiener[28] was controlled by 50 units of insulin 3 years after the episode of insulin resistance, and the patient of Glassberg, Somogyi and Taussig[12] took 50 units for 14 years after recovery from the insulin-resistant state.* All of those patients were mildly diabetic before the phase of insulin resistance, requiring only small amounts of insulin to

* End-results on last 2 cases cited by Glass, Spingarn and Pollack.[11]

remain sugar-free. Only the patient reported by Glass, Spingarn and Pollack[11] remained a mild diabetic after recovery from insulin resistance. In view of the findings reported by the author[17] that animals immunized by thyroglobulin become permanently myxedematous, one may speculate that patients immunized by insulin (insulin-resistance) may completely lose the capacity to produce insulin and thereby become total diabetics. If this is true, then such complete diabetics apparently require 50 to 60 units of insulin daily (Table 1). Stated another way, non-diabetic persons produce about 50 to 60 units of insulin daily.

Conclusions. 1. Antibodies to insulin appear to be antihormonic.

2. Insulin resistance is dependent upon the appearance and concentration in the body of antibodies to insulin.

3. The return of normal insulin sensitivity is dependent upon the disappearance of the immune response.

4. Repeated administration of insulin, rather than its omission, offers a means for overcoming insulin resistance.

5. Antibodies to insulin simulate antibodies to other hormones by being hormone-specific rather than species-specific.

6. Patients recovering from insulin resistance usually become severe diabetics, requiring 50 to 60 units of insulin daily. It is suggested that this represents the level of complete diabetes.

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THE USE OF GLYCOL VAPORS FOR BACTERIAL CONTROL IN LARGE SPACES*

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The bactericidal effect of germicidal mists and vapors on air-suspended microörganisms has now been well established and demonstrated by many investigators.[1,4,7,11] As a result of recent studies it appears that propylene or triethylene vapor offers certain advantages over the use of aërosols and mists previously advocated.[3,8,9,10] The glycols in vapor form are effective in such low concentrations as to be imperceptible in the treated space; they are odorless and non-toxic in the recommended quantities, and the amount necessary to produce air sterilization is so small that the cost is minimal.

Most studies up to this time have been carried out in small test chambers with little accurate data available on large spaces. The chief obstacles to more careful study and application of glycol control of airborne infections in a practical way have been the absence of effective and simple methods of introducing and maintaining adequate concentrations in the desired space and the knowledge of distribution of the vapor in the space. This study reports findings on the distribution. Further information on the apparatus for glycol introduction will be published shortly.

Materials and Methods. *Location of Tests.* All our studies were carried out in a special air-conditioned room (Fig. 1) which was constructed for ventilating research at Northwestern Technological Institute. This room, 38 feet long, 17 feet wide, and 16 feet high, has a volume of approximately 10,000 cu. ft. The walls, ceiling, and floor are cork construction for insulation, and the doors and windows are equipped with refrigerator type doors. For these experiments the ducts leading to and from the air-conditioning apparatus were sealed off.

Glycol Sampling. The glycol determinations were made on 2 liter samples of room air when propylene glycol was analyzed and on a 1 cu. ft. sample of room air when triethylene glycol was used. For the propylene this quantity was obtained by means of a pump displacing 2 liters of water in 10 minutes from one container to another, the air to be analyzed being bubbled through 10 cc. of distilled water with the aid of a sintered glass disperser. When triethylene glycol was recovered a gas flow-meter replaced the water bottles and 1 cu. ft. of air taken over a period of 10 minutes. Samples were obtained at floor level and at 5 and 10 foot levels at opposite ends of the room and at the center walls.

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Analyses were made by the methods described by Puck and Wise, using ceric sulfate for the propylene and potassium dichromate for the triethylene.[6] They were recorded as milligrams of glycol per liter of air.

Introduction of Vapor. Several methods for the production of glycol vapor were used in this study. An air scrubber was constructed, in which room air was blown through a spray of liquid glycol. The droplets were eliminated by a series of baffles and filters, permitting only the vaporized glycol to escape

FIG. 1.—Test-room showing sampling apparatus, atomizer and circulating fans.

with the carrier air. This proved to be a very satisfactory apparatus. Another method consisted of blowing room air over the surface of heated glycol. Finally, glycol-water solutions of definite concentrations were heated to their boiling point and thus vaporized into the room.*

* A detailed discussion of the construction and operation of these devices is soon to be published. All methods could be controlled so that the quantity and rate of emission of glycol vapor were regulated within close limits. Both the air scrubber and boiling devices are satisfactory for large scale installation.

Means of Air Agitation. Glycol samples were taken when there was no air movement in the room and when air was agitated to varying degrees by means of circulating fans (Fig. 1).* The speed of the fans could be regulated by a variable transformer and the direction of air flow controlled by adjusting the angle of the fan-head. Agitation was also produced by the 100 cu. ft. per minute blower incorporated in the air scrubber.

Bacterial Samples and Counts. Test organisms used were *Staphylococcus albus* and a guinea pig strain of hemolytic streptococcus (Streptococcus C). The suspensions of organisms were prepared by concentrating 50 cc. of an 18 hour culture of the desired bacteria and resuspending the organisms in saline to a standardized concentration, 1 cc. of the suspension containing 1 billion organisms. This was then centrifuged, the supernatant fluid decanted, and the organisms again suspended to their previous volume with filtered saliva. Saliva was used as the diluent since it has been noted that organisms suspended in this material remain in the air much longer than those introduced in broth or saline and we wished to simulate field conditions as closely as possible. The suspensions were sprayed by means of a modified Graeser atomizer[2] which produced an extremely fine mist.

Bacterial samples were obtained by the use of the apparatus described by Moulton;[5] 1 cu. ft. of air was drawn through 10 cc. of broth in the reservoir and 0.5 and 1 cc. samples were plated. Colony counts were made in the usual manner and recorded as numbers of organisms per cubic foot of air. Samples were taken in the same positions as those for glycol analysis, that is, at floor, 5-foot and 10-foot levels at opposite ends and the center of the room.

A test was run as follows: the room was first thoroughly aired out by opening the windows and doors and turning on the two large circulating fans. It was then made air-tight and 10 cc. of the bacterial suspensions were sprayed directly under the two circulating fans revolving at medium speed (1350 r.p.m.) at the two opposite sides of the room. Simultaneous samples were taken immediately after the cessation of the spray and at intervals of 15 minutes for a total period of 2 hours. The doors and windows were reopened, the fans speeded up and the room allowed to air for 1 hour. The room was again sealed, the glycol vapor introduced, and 10 cc. of the same bacterial suspension used for the control test was sprayed under the fans. Simultaneous samples of both glycol and bacteria were taken as described.

Control of Humidity. Since small quantities of glycol may collect on the hairs or fine strands of the usual type of humidistat, all observations on humidity were taken by means of wet and dry bulb thermometers. Although the scrubber and boiling apparatus were able to maintain humidity fairly well it was sometimes necessary to introduce additional water vapor into our room, since it has been observed that in order to obtain optimum bactericidal effect from the glycol vapors a humidity of 35 to 40% is desirable. The additional water vapor was added either by heating a container of water or by introducing steam in small quantities.

Data. *Distribution Studies.* Our first object was to determine if it were possible to build up an adequate glycol concentration in a space of 10,000 cu. ft. and maintain it for long periods. This can readily be done and may be produced by any of the methods described, taking 30 minutes to 1 hour depending on the apparatus used. However, the necessity of maintaining adequate humidity causes certain limitations of methods of introduction.

An adequate glycol concentration may be attained theoretically in a space with no air agitation by allowing the vapor to diffuse slowly throughout the room. However, it would appear from repeated observations that some means of air agitation is necessary to produce uni-

* We wish to acknowledge the coöperation of the Reynolds Electric Company, Chicago, Ill., in supplying us with these fans.

form and rapid distribution. This is particularly true if the space is irregular in shape.

TABLE 1.—RATE OF FALL OF PROPYLENE GLYCOL IN TEST-ROOM

Time	Glycol concentration in room air (mg. per liter)		
	At floor level	At 5 feet	At 10 feet
Generator off	0.195	0.202	0.269
2 hours later	0.196	0.149	0.145
4 " "	0.148	0.110	0.110
6 " "	0.132	0.106	0.105
24 " "	0.048	0.048	0.037
26 " "	0.063	0.052	0.052
28 " "	0.032	0.040	0.028
30 " "	0.036	0.017	0.026

The rate of fall in concentration of glycol in the air was determined for our test chamber, and a typical experiment is shown in Table 1. These values were obtained in the following manner: glycol vapor was introduced into the room and samples were taken until a satisfactory concentration of glycol in the air was reached. The glycol "generator" was then turned off, the room sealed, and air samples taken at the intervals shown in the table. The concentration held up quite well as might be expected in this space. It was of interest also to note that with very gentle air agitation there was no evidence of stratification of glycol vapor in our room (Table 2). The samples taken at floor level, at 5 feet, and at 10 feet were all of equal magnitude. We should also like to point out that even though the space was relatively air-tight it was necessary to introduce a glycol concentration from 50 to 100% greater than the ultimate concentration desired in the room to compensate for exfiltration of air.

TABLE 2.—DISTRIBUTION AND CONCENTRATION OF PROPYLENE GLYCOL IN TEST-ROOM

Time	Glycol concentration in room air (mg. per liter)			Mg. glycol per liter in air delivered from generator
	At floor level	At 5 feet	At 10 feet	
Glycol generator operating for				
1 hour	0.090	0.083	0.087	0.229
1 hour later	0.127	0.138	0.107	0.312
2 hours later	0.125	0.182	0.125	0.307
3 " "	0.207	0.164	0.185	0.326

Although the figures recorded on these protocols are for propylene glycol, repeated tests using triethylene glycol showed no difference in the behavior of this vapor in the atmosphere.

Bacterial Studies. As a further "check" of the distribution, tests on the bactericidal action of the glycol vapor were made. We were interested in obtaining the immediate killing effect rather than death after prolonged periods of exposure. It was found that whereas in small chamber experiments immediate killing occurred with concentrations of 0.02 mg. of propylene glycol per liter, a concentration of 0.2 mg. per liter was necessary in the large test-room. When triethylene glycol was used an immediate and striking effect was produced in our space

with a concentration of 0.005 mg. per liter.* The following 2 protocols (Tables 3 and 4) illustrate our findings. Photographs of these data are shown in Figures 2 and 3.

TABLE 3.—EFFECT OF PROPYLENE GLYCOL VAPOR ON STREPTOCOCCUS C

Vapor concentration	Humidity (%)	Time interval of samples (after spraying)	No. colonies per cu. ft.	
			Control	Test
0.2 mg. per liter	42	Immediately after	4166	0
	42	15 minutes later	3120	0
	42	30 " "	1760	0
	42	60 " "	442	0

It was observed that in order to produce this effect with either glycol a humidity of about 40% was necessary. When the humidity was lower or when the concentration of glycol in the air was lower, definite reduction of bacterial counts could be produced with no recovery of viable organisms after periods of 30 minutes to 1 hour after exposure. However, for the purpose of adequate and preliminary wide scale testing we felt that the immediate killing effect should be sought. This is perhaps a higher concentration than might ultimately be desired.

TABLE 4.—EFFECT OF PROPYLENE GLYCOL VAPOR ON *Staphylococcus albus*

Vapor concentration	Humidity (%)	Time interval of samples (after spraying)	No. colonies per cu. ft.	
			Control	Test
0.2 mg. per liter	41	Immediately after	9750	0
	41	15 minutes later	9360	0
	41	30 " "	9260	0
	41	60 " "	3220	0

Discussion. Since we have observed that there is ready diffusion of vapor about the space to be treated it would theoretically be possible to introduce glycol vapor into a space and allow it to distribute itself spontaneously. However, from a practical standpoint this would never be adequate to insure uniform distribution due to air currents in and out of the space and leakage of air out of the space. Thus it is necessary to have some means of air agitation. This may be produced either by the presence of circulating fans or by a simple duct system. The size, speed, number, and position of the circulating fans must be determined by the physical characteristics of the space to be treated. For portable and emergency use this type of fan is the simplest and easiest to use.

When a more permanent installation is feasible a duct system may be constructed. Since glycol is a relatively inert substance the construction of these ducts may be simple. They may be made of almost any structural material ranging from fiber board (masonite) to metals. An example of this type of duct layout is shown in Figure 4. Observe that a duct leading outside is installed. The quantity of outside "fresh air" introduced may be regulated by a damper. Our plans have contemplated 10 cu. ft. per minute for each individual in the space but

* Misunderstanding and confusion have arisen from the expression of glycol concentration in "parts per million" used in previous publications. For this reason we suggest the use of weight per volume (milligrams per liter of air). This may be converted to grams per million cc. of air if one so desires, for comparison with published data.

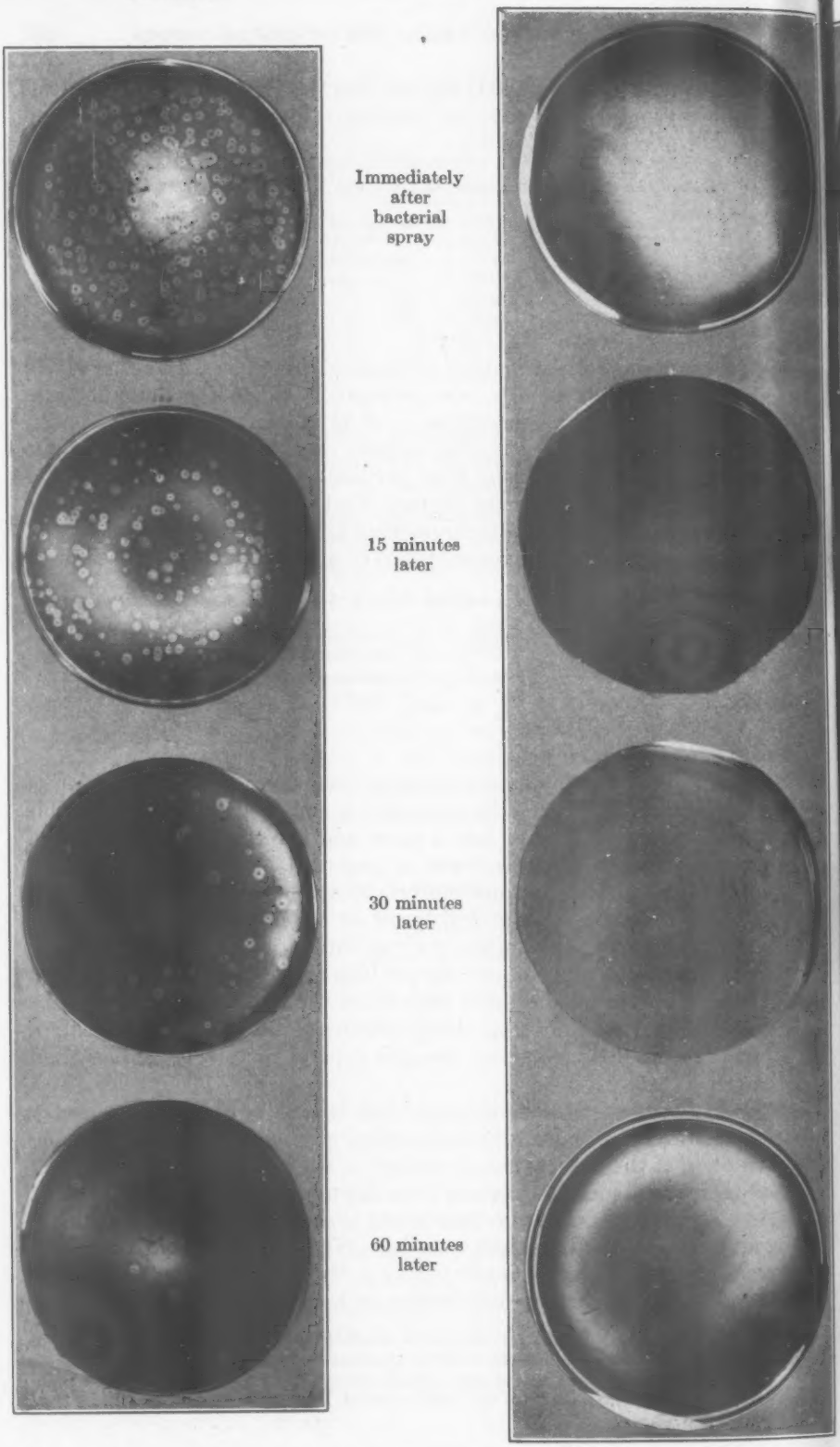

FIG. 2.—Bacterial plates showing colony counts (Streptococcus C) obtained in experiment shown in Table 3.

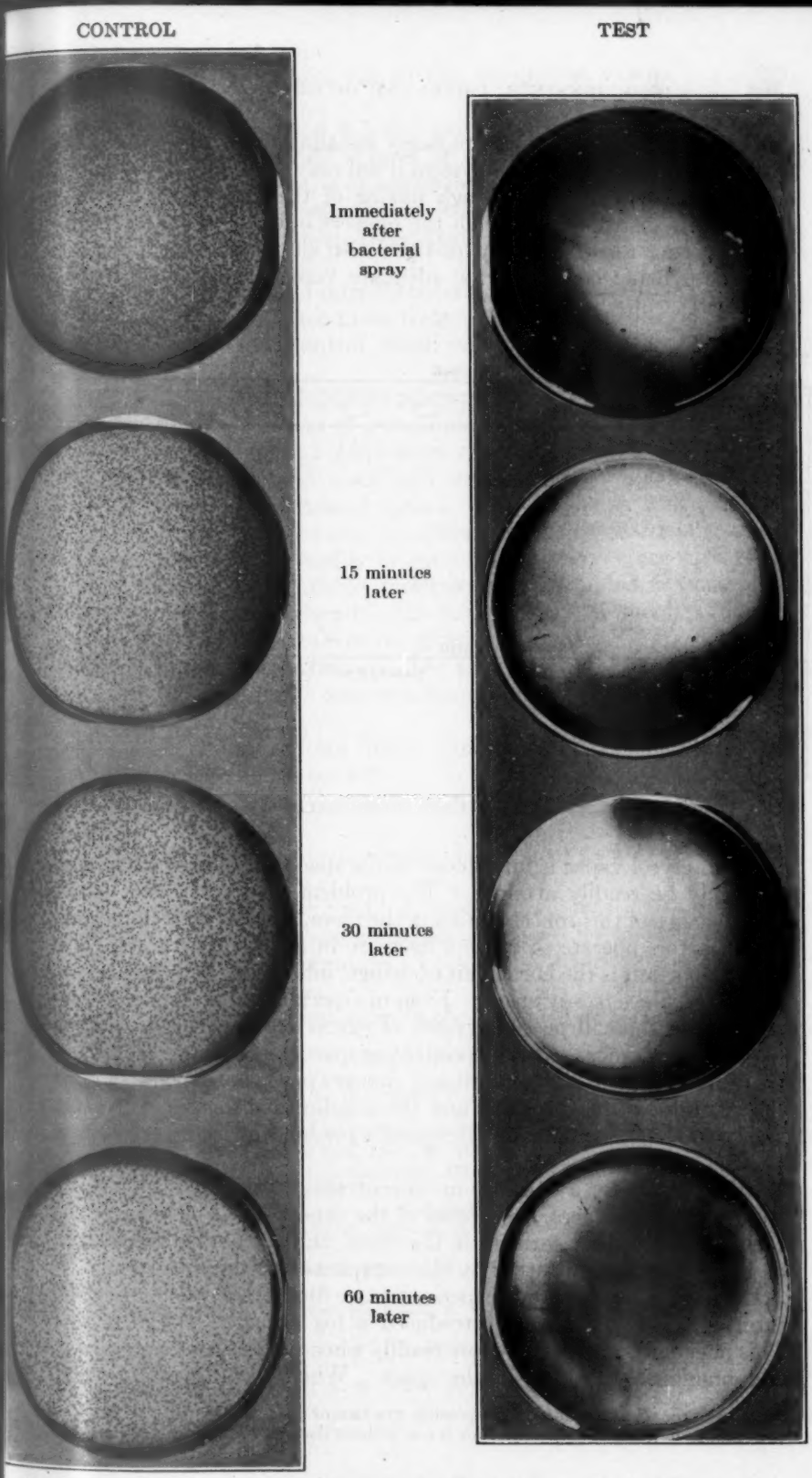

FIG. 3.—Bacterial plates showing colony counts (*Staphylococcus albus*) obtained in experiment shown in Table 4.

this amount may be reduced in many installations. If this untreated air is introduced in the duct system it not only affords fresh air for the occupants but enables thorough mixing of the glycol vapor with it before it is distributed through the blowers into the room. Thus we would have a room relatively air-tight with all outside air coming into the space being controlled for adequate volume and glycol concentration.

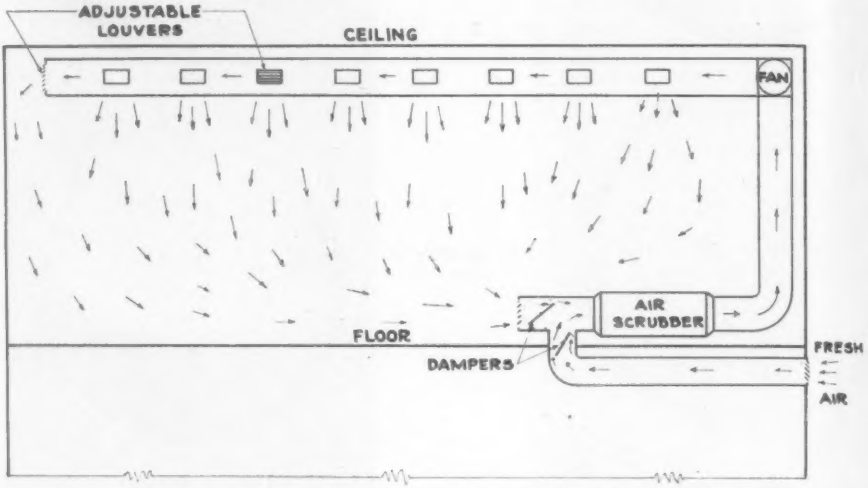

FIG. 4.—Layout of duct system for distribution of glycol vapor.

When glycol vapor is introduced into a space the desired concentration may be readily attained. The problem then to be met is the maintenance of this concentration in the room. It has been found that many factors operate to cause a decrease in this concentration. The most important is the normal air exchange, infiltration and exfiltration, that takes place in any space. Even in especially built chambers constructed so that all possible points of egress are sealed it is difficult to prevent air exchange. In normal living spaces under windy conditions this air exhange may be as high as 8 changes per hour, depending upon the tightness of construction and the number and locations of doors and windows. Normally the air changes per hour lie in the range from $\frac{1}{2}$ to 3.

Other causes for a decrease in concentration are condensation of the vapor on cold surfaces, absorption of the vapor by the clothing of the occupants and other surfaces in the room, and the actual metabolism of glycol which might occur by the occupants breathing the air.

During the course of our experiments we found that when air supersaturated with glycol was introduced a fog occurred in the room.* This phenomenon occurred more readily when the temperature was low and humidity was high in the space. When the concentration of

* In the course of a study on the possible fire hazard produced by the glycols it has been found that this supersaturated air is not without danger. These data are in press.

propylene glycol was over 0.5 mg. per liter, or the concentration of triethylene glycol reached a level of about 0.01 mg. per liter, fog resulted. This, of course, is objectionable in occupied rooms and limits the method of glycol introduction as well as necessitating careful control of concentration. Further observations on fog formation are being carried out.

Thus the actual rate of introduction of glycol into any space must be determined for each space to be treated. We have developed several means for automatic control which will be reported in subsequent publications.

The necessity for maintaining adequate humidity also raises certain difficulties in the problem of maintaining bactericidal activity. Since the greatest incidence of respiratory disease occurs during the cold periods of the year and since cold weather is accompanied by low relative humidities in heated spaces, water vapor as well as glycol vapor must be introduced into the space. If an air-conditioning unit is in operation this may readily be attained; however, since such apparatus is not usually available, moisture must be added in some other way. It may be introduced in the form of steam or may be produced along with the distribution of the glycol vapor.

Summary and Conclusions. 1. The production and maintenance of glycol vapor in adequate concentrations in large spaces is possible and readily attainable.

2. Glycol vapor diffuses freely throughout large spaces and no stratification of the gas occurs.

3. Some means of air agitation is desirable to insure adequate distribution.

4. Bactericidal activity occurs in large spaces as well as small test chambers.

5. Concentration of 0.2 mg. per liter of propylene glycol and 0.005 mg. per liter of triethylene glycol are necessary for immediate killing of the air-borne microörganisms. Lesser concentrations may suffice to control air-borne disease.

6. Maintenance of humidities in the region of 40% is necessary.

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INFLAMMABILITY CHARACTERISTICS OF PROPYLENE GLYCOL AND TRIETHYLENE GLYCOL IN LIQUID AND VAPOR FORM*

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The recent observations on the effectiveness of certain glycol vapors in bringing about striking air sterilization present a most promising method for the control of airborne disease. It has been shown that the use of those substances, particularly propylene glycol and triethylene glycol, offers definite advantages over measures previously described. Bactericidal and virucidal concentrations of propylene or triethylene glycol vapor are odorless, non-toxic, effective in extreme dilutions, easy to distribute and reasonable in cost.[1]

In view of the possible widespread use of these materials as a means of prevention and control of airborne infection the following study was carried out to ascertain the fire hazard which might be created by their presence.

Since glycols are highly hygroscopic and freely miscible with water, one must assume that only rarely will water-free, 100% glycol be present except in storage. The glycol condensed on surfaces, that is, walls, ducts, windows, and so forth, will contain water, the proportion of water in the condensate being dependent upon the relative humidity and temperature of the space treated and the temperature of the condensing surfaces themselves.

Propylene Glycol. The physical properties of propylene glycol are as follows: Molecular weight, 76.06; boiling point, 368° F. at 14.7 p.s.i.; specific gravity, 1.0381; vapor pressure, 0.18 mm. Hg at 68° F.; and pounds per gallon, 8.64. Flash point data (furnished by the Carbide and Carbon Chemicals Corporation) determined by means of the open cup method, are as follows: 100% glycol flashes at 220° F.; 95% at 225° F.; 90% at 245° F.; 85% or lower—no flash point is evident.

Experiments Conducted. *Open Dish Tests.* Varying glycol-water solutions were placed in small evaporating dishes and the flame of a Bunsen burner was allowed to play over the surface of the fluid mixture. After about 60 seconds of heating, the contents of the dish containing 100% propylene glycol could be ignited and it burned with a blue flame until all of the liquid was consumed. A 90% mixture could also be ignited, although the flame had to be held over it for 2 or 3 minutes. An 80% mixture burned with even greater difficulty, requiring 4 to 5 minutes to ignite. Using 75% glycol, the mixture was ignited but after a few minutes the flame spontaneously went out. Mixtures containing 70% glycol or less could not be ignited unless they were violently boiled for a few minutes. It would appear that the more concentrated solution, resulting from the loss of water vapor, alone was inflammable.

* The work described in this paper was done under a contract, recommended by the Committee on Medical Research between the Office of Scientific Research and Development and Northwestern University.

Asbestos Wick Tests. Using a like series of concentrations as in the previous tests, asbestos wicks were wetted with the appropriate solution and ignited by means of a Bunsen burner flame. Results very similar to those described with the open dish were obtained; that is, as the amount of water in the solution was increased it became more and more difficult to ignite the wick. The 75% solution did not propagate flame, and lesser solutions were non-combustible.

Match Tests. When lighted matches were dropped into varying solutions, a slight flame about the match persisted for a few minutes with 100% glycol, but no flame occurred with solutions of 90% glycol or less.

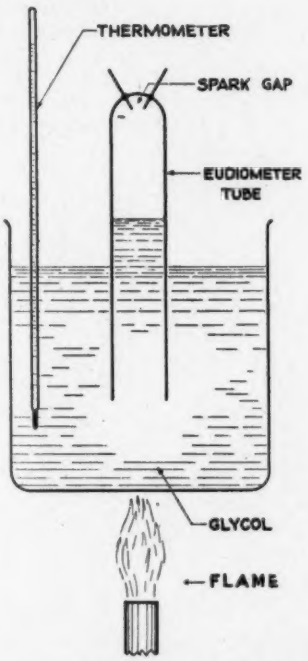

FIG. 1.—Eudiometer submerged in basin of glycol for vapor explosion test.

Fabric Tests. Silk, rayon, wool and cotton were immersed in varying solutions. If these materials were allowed to dry (to the touch) there was no increase in their combustibility. However, when wet with the solution they behaved as did the asbestos wicks except that in these cases the material itself also contributed to the combustion.

Spark Tests. It was impossible to ignite 100% glycol at room temperature by means of a spark produced by a spark coil.

Eudiometer Studies. A short eudiometer (Fig. 1) was arranged for immersion in a beaker containing 100% glycol solution. The eudiometer was partially filled with air and a spark was sent across the gap by means of a high-frequency induction coil. An explosion of the gas could not be obtained until the temperature of the liquid reached 214° F. If the liquid contained as little as 5% water, no explosion of the resulting vapor could be obtained. It was calculated that the concentration of propylene glycol in the explosive gas mixture was 85.5 mg. per liter.

Flame Propagation of Unheated Glycol. A film of 100% glycol was spread on a stone surface and a lighted match was placed at one end. The match burned for about 10 seconds, then went out spontaneously. A long stream of

the same material was also spread on a stone surface and again there was no spread of flame, the match going out after 60 seconds.

Condensation Studies. To determine the actual concentration of condensates occurring in conditions simulating field conditions, the apparatus shown in Figure 2 was constructed. Air was first humidified by bubbling it through water; it was then passed over an aqueous glycol solution which was warmed in a constant temperature bath. The resulting gases were then introduced into a glass chamber of 2 cu. ft. capacity. The humidity of the incoming air, as well as its glycol concentration, was regulated by changing the temperature of the water-bath or by increasing the percentage of water in the glycol-water solution. The atmosphere of the chamber was agitated by means of a small, 3-inch fan, and the humidity was determined by means of a wet-dry bulb thermometer. Two-liter samples of the chamber air were withdrawn for glycol analyses.

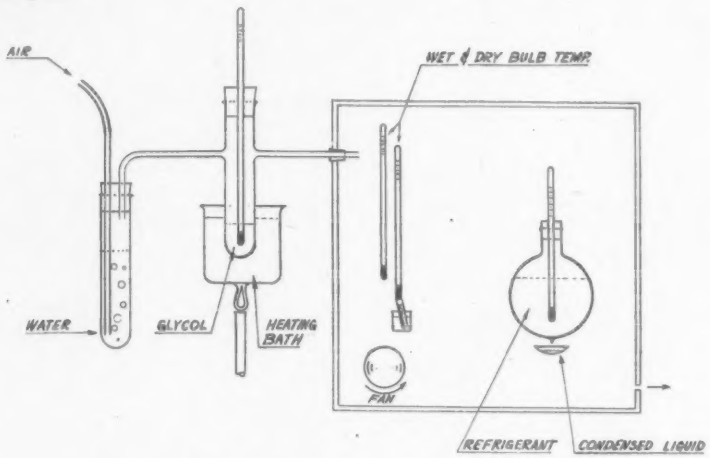

FIG. 2—Determination of concentration of condensates.

TABLE 1.—CONDENSATION STUDIES

Propylene glycol concentration (mg. per liter)	Chamber humidity (%)	Chamber temperature (°F.)	Condenser temperature (°F.)	Condensate concentration (%)
0.149	60	78	32	5.0 glycol
0.169	50	78	32	11.5
0.170	37	82	32	3.0
0.208	43	82	32	5.0
0.211	47	76	32	16.0
0.217	53	78	32	5.0
0.162	46	78	0-32	5.0
0.172	60	79	0-32	5.0
0.186	60	80	0-32	6.5
0.196	60	75	0-32	17.0
0.251	44	79	0-32	31.5
0.290	64	78	0-32	7.0
0.300	52	79	0-32	16.1
0.310	61	79	0-32	7.2
0.323	60	78	0-32	6.0

A standard 1-liter, round-bottomed flask was suspended in the chamber. A teat was fused to the bottom of the flask, allowing the condensate to drop into a watch crystal placed beneath. The flask was then filled with ice and, to obtain lower temperatures, with salt-ice mixtures. The samples of condensate were analyzed for glycol content by means of refractive indices. Observations are listed in Table 1. It may be seen that in a space, the humidity range

of which is 37 to 61%, with a temperature as high as 82° F., containing a condensing surface as low as −32° F., and filled with a maximum of 0.323 mg. of propylene glycol per liter, no inflammable condensate results. This is particularly striking since adequate bactericidal action occurs in air containing 0.1 mg. propylene glycol per liter.

Triethylene Glycol. The physical properties of triethylene glycol are as follows: Molecular weight, 150.17; boiling point, 548° F. at 14.7 p.s.i.; specific gravity, 1.1254; vapor pressure, 0.01 mm. Hg at 68° F.; and pounds per gallon, 9.37. Flash point data furnished by the Carbide and Carbon Chemicals Corporation, determined by means of the open cup method, are as follows: 100% glycol flashes at 330° F.; 95% at 345° F.; 90% or lower, no flash point is evident.

Tests on inflammability using the open dish method, flame propagation, fabric wicks, spark coil and matches, gave results practically identical with propylene glycol. In the eudiometer an explosion occurred at 356° F. with a calculated vapor concentration of 130 mg. per liter. If any water were present in the glycol no explosion could be obtained.

Discussion. Since the concentration of propylene glycol and triethylene glycol vapor necessary for bactericidal action is 0.1 mg. per liter and 0.005 mg. per liter, respectively, it is obvious from the above observations that there is no hazard produced by the presence of this quantity of vapor in the air. In the case of propylene glycol, 855 times this amount is necessary to produce an explosive mixture, and for triethylene glycol 26,000 times this quantity must be present. This explosive property, however, must be considered if an apparatus introducing superconcentrated gaseous mixtures is used, for at the point of exit of the gas such a concentration might possibly be attained.

The possibility of danger arising from the condensation of glycol on cold surfaces in the treated space must be considered even though, as has been shown, using the maximum glycol concentration plus a high humidity and low temperature on the condensing surface, very dilute aqueous solutions of glycol were obtained. It would appear that since relatively intense and prolonged application of heat is necessary to ignite solutions containing as little as 30% water, there is little chance for glycol condensates to burn in ordinary use. If, however, a fire should occur in such a treated space due to other causes, the heat produced would probably bring about the loss of water from the condensate and thus the glycol might add to the general conflagration, just as the other objects or material present, that is, woodwork, bedclothing, and so forth.

Another source of danger would be at the area of storage of the glycol; here, too, if intense and prolonged heat were applied, fire might occur. It might be noted that this danger is no greater than that produced by the storage of other combustible materials, such as fuel oil. This hazard could be reduced by storing the glycol, not as 100% material, but as aqueous solutions containing as much as 20% water.

There would appear to be little difference between propylene glycol and triethylene glycol as far as fire hazard is concerned. According to the code of the New York City Fire Department, pure propylene glycol is classified as not combustible but inflammable, and triethylene as neither combustible nor inflammable. The smaller quantities of triethylene glycol necessary to produce sterilization of the air neces-

sarily results in a lesser amount of condensed glycol or surfaces. This is a matter of degree, particularly of time during which the substance is used.

Conclusions. 1. In the vapor-phase concentration required for air sterilization, propylene and triethylene glycol offer no fire or explosive hazard.

2. The addition of water to these substances greatly reduces the possible fire hazard produced by their presence in storage or vaporizing devices.

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THROMBOPHLEBITIS AS A HITHERTO UNREPORTED COMPLICATION OF THIOCYANATE THERAPY OF HYPERTENSION

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In the past 3 years we have treated 40 cases of essential hypertension with potassium thiocyanate.[2] These cases were carefully studied, including frequent blood thiocyanate levels, according to the method of Barker.[1] The clinical results of these studies are reported elsewhere.[2]

The purpose of this paper is to report on the occurrence of thrombophlebitis as an apparently unpublished complication in the administration of potassium thiocyanate.

Of the 40 patients treated, 4 exhibited this complication. Such high incidence makes us feel that it is not a mere coincidental finding but a definite toxic effect.

The usual toxic effects that have been reported are dermatitis, weakness, dizziness, loss of appetite, and easy fatigability. Angina pectoris in the course of therapy has also been reported.[3] We have observed 1 case of coronary thrombosis in a patient taking the drug, but this complication is not so very unusual in the course of untreated hypertension. Venous thromboses in the extremities have never, to our knowledge, been previously reported.

Case Studies. Of the 4 cases observed we shall report in detail the following one:

Case 1. B. R., a white male, age 51, was first seen in the clinic on Dec. 28, 1937. He was admitted with complaints of generalized throbbing headaches, poor memory, dizziness, dyspnea, orthopnea, palpitation, precordial pain, nocturia and fatigue.

The blood pressure on admission was 238/130. A 6-foot film revealed the heart to be enlarged in all diameters, accentuation of the left ventricular curve, and dilatation and tortuosity of the aorta. The electrocardiogram showed deviation of the electrical axis to the left. A pyelogram made at another hospital had been reported as showing some shagginess of the calyces

of the right pelvis. Intravenous pyelography performed when patient was admitted to the ward revealed both kidneys to be normal in size, shape and position. The pelves, calyces and ureters were normal bilaterally. The blood Wassermann was negative, the hemoglobin 85%, red blood cells 4.65 million, white cells 6600 per c.mm., with 80% polys and 20% lymphocytes. The non-protein nitrogen of the blood was 31 mg. per 100 cc., the creatinine 2, and the uric acid 3.6. The urine revealed a specific gravity of 1.018 and contained a trace of albumin. Occasional hyaline and granular casts were seen on microscopic examination, as well as an occasional red blood cell and 2 to 3 white cells per high-power field.

After a period of observation of slightly over 3 years, during which time the blood pressure was persistently at a high level with the systolic at 190 to 260 mm. Hg and the diastolic at 130 to 150 mm. Hg, he was started on potassium thiocyanate therapy. The initial dose was 0.1 gm. 3 times a day, and after a week a blood level of 4 mg. thiocyanate per 100 cc. was reached. The blood pressure, however, remained at 257/140. On the same dose, a week later, the blood pressure was 232/140 and the blood thiocyanate, 4.2 mg. per 100 cc.

A slight dermatitis of the scalp was noted but it was decided to continue the thiocyanate therapy and the dose was increased to 0.2 gm. 3 times daily. A week later the determination of thiocyanate in the blood showed a level of 6.9 mg. per 100 cc., but the blood pressure remained elevated, the systolic being 226 and the diastolic 130. The dermatitis had cleared and the patient claimed to be subjectively improved, stating that the severe headaches had abated. The dose was increased again to 0.3 gm. thrice daily. There was no increase in the blood thiocyanate, the concentration remaining at 6.45 mg. per 100 cc. The blood pressure was still high so he was given 0.4 gm. 3 times a day, a total of 1.2 gm. daily. This time a blood level of 10.8 mg. was reached. There was no perceptible lowering of the blood pressure. The dose of 1.2 gm. daily was continued for 2 weeks when he began to show some nausea and loss of appetite and it was decreased to 0.3 gm. daily, lowering the concentration of thiocyanate in the blood to 5.5 mg. per 100 cc. The blood pressure had not been lowered at all but the patient stated that he felt better while on the medicine. It was therefore continued. After having received thiocyanate for 6 months he developed a thrombophlebitis in the left leg. Since there had been no objective evidence of clinical response to the thiocyanate therapy, the drug was discontinued and the phlebitis treated with rest and cold application. The acute inflammatory symptoms subsided readily, but the superficial veins could be palpated as hard cords.

Now the patient began to complain of a return of his headaches, dizziness, and visual disturbances consisting of seeing "snow falling." When all evidence of acute inflammation had subsided the thiocyanate treatment was reinstituted and within a month he presented evidence of phlebitis in the other leg. The thiocyanate was again discontinued, and started again after acute inflammation had subsided. Four months later there was a reappearance of the phlebitis in the right leg and also evidence of inflammation and thrombosis in and around the veins of the right arm and forearm. This time the drug was discontinued and has not been resumed. The patient is still under treatment and is running a consistently high blood pressure of about 250 mm. Hg sytolic, and 150 mm. Hg diastolic.

In addition to the above case thrombophlebitis was also encountered in 3 other cases in our series. Short summaries of these cases are herewith presented:

CASE 2.—M. J., a colored female, age 64, was started on potassium thiocyanate on Oct. 11, 1940. The blood pressure at the start of treatment was 230/120. On a dose of 0.1 gm. 3 times a day the blood thiocyanate level was 19 mg. per 100 cc. and it was decreased to 0.1 gm. twice daily, when the concentration in the blood was reduced to 12.5 mg. On April 8, 1941, the blood

pressure had been reduced to 170/110, but a phlebitis of the veins about the left ankle was discovered and the drug was discontinued.

CASE 3. M. D., a white female, age 52, was taking thiocyanate for a period of 3 years with a satisfactory lowering of her blood pressure, and maintaining a blood thiocyanate level between 8 and 10 mg. On January 26, 1943, approximately 3 years after she had started taking thiocyanate, there developed a swelling of the left leg with patchy areas of redness and tenderness and the drug was discontinued.

CASE 4.—H. S., a white male, age 71, was given potassium thiocyanate in a dose of 0.1 gm. 3 times a day and after 1 week showed evidence of thrombophlebitis. The drug was discontinued before any blood level was obtained.

Summary and Conclusions. Four cases of thrombophlebitis are reported as occurring in the course of therapy of hypertension with thiocyanate, an incidence of 10%. This high frequency is much greater than can be explained on pure coincidence and must be accepted as a toxic effect which has not been previously reported.

It does not appear to be related to the level of thiocyanate in the blood, and may occur early or late in the course of treatment.

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A CASE OF ACUTE MENINGITIS CAUSED BY NEISSERIA PERFLAVA

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IN the winter and spring of this year, meningococcus meningitis assumed epidemic proportions and a considerable number of cases was seen at this hospital. The effectiveness of sulfonamide was striking. Consequently, it became important to us to investigate thoroughly any cases in which therapy failed. One such case was seen early in its course, was treated with large doses of sulfapyridine and finally with antimeningococcus serum and, nevertheless, resulted in a fatality. Cultural examination of the organism obtained from the spinal fluid has demonstrated that it is not a meningococcus but a chromogenic diplococcus of the pharyngeal group, and by its fermentation reactions is classified as *Neisseria perflava*. Cases of meningitis caused by pharyngeal Neisseria have been reported occasionally[2,3,4] and a group of 14 cases from one outbreak of meningitis was reported by Branham.[1] Since these organisms are serologically distinct from the meningococcus, antimeningococcus serum is ineffective. In our case, chemotherapy by the sulfonamide group was unsuccessful.

Case Study. R. J., a 31 year old merchant seaman, was admitted to the hospital late on the night of April 25, 1943. He seemed acutely ill, had hallucinations and tremor and gave a history of recent alcoholic intoxication. The nose and throat were congested and the temperature was 37.6° C. During the following 24 hours, his mental condition became worse and he began

to thrash around restlessly with rolling eyes. Examination did not reveal any injury to the head or body. The pulse was 140 and temperature 38.2. Several small red spots (petechiæ) were noted in the skin of the abdomen and chest. Positive Babinski, Oppenheim and Gordon signs were found on the left side, a partial Babinski on the right side and the Brudzinski tests were positive on both sides. There was extreme rigidity of the neck and the Kernig sign was positive. The patient responded only to painful stimuli.

Spinal tap was done on April 27. The fluid was cloudy and greenish. The initial pressure was 220 cm. This fluid revealed cell count of 15,000, mostly neutrophils. Gram-negative intracellular diplococci were present. These organisms appeared larger than the usual strain of *Neisseria intracellularis*. Six gm. of sulfapyridine were administered intravenously followed by 1 gm. every 4 hours for a total of 21 gm. During the next 24 hours, he also received 120 cc. of antimeningococcus serum. A second spinal tap revealed increased cloudiness of the fluid. The color was greenish-yellow and the pressure 250 cm. Since the clinical condition was deteriorating, 20 cc. of antimeningococcus serum was administered intraspinally on April 29. The temperature continued to rise on the 29th, passing 40° C., and on the 30th, reached 41.8°. Death occurred late that night, 5 days after admission.

Autopsy revealed no essential morbid processes except in the head. A very thick, greenish-yellow exudate was found closely attached to the base of the brain from the region of the optic chiasm back to the medulla. In places, the exudate was 1.5 cm. thick and on section revealed cavitation with free pus enclosed in the pia-arachnoid.

In the routine examination of the base of the skull, it was apparent that the thickest exudate was localized around the pituitary. When this was removed, an oval fenestration in the floor of the pituitary fossa was revealed, measuring approximately 4 mm. in diameter. Its edges were smooth and through it the interior of the sphenoid sinus was plainly visible. No other lesions or defects of the skull were found. The contents of the sphenoid sinus consisted of thin mucus without gross pus.

Microscopic examination showed an unusually dense exudate of neutrophils in the pia and arachnoid. There was no extension of the exudate around the cortical vessels. A striking finding was the presence of masses of exudate with necrosis and the formation of small abscesses in the anterior lobe of the pituitary. This unusual site and the intensity of the inflammatory process in this area supported the conjecture that the portal of entry was the defect in the floor of the pituitary fossa.

The spinal fluid and the exudate at the base of the brain were cultured on the modified McLeod medium used for Neisseria in this laboratory. An abundant growth of greenish-yellow, slightly raised discrete colonies developed in 24 hours. Even at this early period, the chromogenesis was apparent. Fermentation was noted in media containing dextrose, maltose, levulose, sucrose and mannitol. The organism showed no agglutination by polyvalent anti-meningococcus serum.

Discussion. Branham,[1] commenting on the significance of atypical Neisseria as the causative agents of meningitis, states, "The natural habitat of the genus Neisseria, other than the gonococcus, is the nasopharynx. Meningeal invasion by any of these other than the meningococcus is only of occasional occurrence." However, her report of 14 cases caused by a homogeneous group of chromogenic Neisseria leads one to believe that the pathogenic activity of these organisms outweighs their biochemical and cultural peculiarities in establishing their identity as meningococci. On the other hand, Wilson and Smith[5] suggest that all Neisseria differing from typical meningococci and gonococci be placed together in one species, *Neisseria pharyngis*. The problem of classifying atypical Gram-negative diplococci is quite

different in meningitis from what it is in case-finding studies in gonorrhea. Although gonococci exhibit constant morphologic and biochemical characteristics, meningococci show variations in regard to fermentation and antigenic composition. Reimann and Koucky[4] cultured from a case of meningitis an organism which was chromogenic, produced acid in glucose and lactose and was not agglutinated by polyvalent antimeningococcus serum. They regard these deviations as "part of the pattern of variation of the bacterium concerned." It seems to us that the inclusion among *Neisseria intracellularis* of organisms differing in fundamental characteristics from the recognized strains leads to confusion. The application of bacteriologic or other scientific systems to medicine is pragmatic, and for the physician the difference between an organism susceptible to a specific serum or chemical and another, however closely related one, insusceptible to these agents is essential.

Summary. A case of acute meningitis is described differing clinically from meningococcus meningitis in failure to respond to sulfonamide and serum therapy. The causative organism was *Neisseria perflava*. It appears that the unusual nature of the invading organism might have been suspected from the pigmentation of the spinal fluid. The portal of entry found at autopsy was a congenital defect in the roof of the sphenoid sinus.

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A CASE OF HISTOPLASMOSIS (DARLING) WITH AUTOPSY

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Histoplasmosis was first described by Darling in 1906 and 1908. Since that time the diagnosis has been made with increasing frequency. In this report the literature will not be reviewed, as this has been done recently by Meleney,[3] Wright and Hachtel,[7] and others, and the cultural characteristics adequately covered by De Monbreun.[1] To those cases already reported in the literature the authors wish to add another.

Case Report. (A–68–42, A.M.M. Acc. 89561, Fort Benning). C. L. P., a 23 year old colored male, a laborer from Alabama, was admitted to the Station Hospital, Fort Benning, Ga., on Oct. 22, 1942. Before coming under observation he had been acutely ill 7 weeks with chills, fever, aching, cough, and blood-streaked sputum. The patient stated that he felt fairly well during the day, but each evening would have chills, fever, aching, and sweats. The cough

with blood-streaked sputum had been present for about a year. The sputum was described as thick, milky white, and occasionally streaked with blood. There had been a 15 pound weight loss in the 7 weeks prior to admission. Shortness of breath had been noticeable for about 2 weeks.

The *family history* was non-contributory. The *past history* was significant in that the patient had had malaria in 1938, and typhoid fever in 1935.

Examination revealed a colored adult male who appeared to be acutely and seriously ill. He appeared toxic and dyspneic. The conjunctivæ were clear; the mucous membranes appeared pale. The tonsils were small; the mouth was foul. No lymph nodes were palpable. The chest was symmetrical, expansion free, but excursions were small. Fremitus over both apices was diminished and the percussion note impaired. Breath sounds were distant, and numerous moist râles were scattered over both lungs. Respirations were 30 per minute. The heart showed no abnormalities except for a tachycardia of 120 per minute. The blood pressure was 94/66 mm. of mercury. The abdomen was distended and tympanitic. The upper abdomen was tender. The liver and spleen extended 2 and 4 fingers breadth below the costal margin respectively. The spleen was tender. The superficial and deep reflexes were bilaterally equal and active.

Laboratory Data. Blood count (10-25-42): R.B.C., 3,100,000 (hemoglobin, 60%); W.B.C., 5000 (polymorphonuclears, 75%; lymphocytes, 23%; monocytes, 2%). No malarial parasites seen on 3 examinations. *Kahn* test negative. *Sputum* examinations on 9 occasions failed to show acid-fast organisms. *Sedimentation* rate (10-25-42) was 27 mm. in 1 hour (Cutler). *Urinalysis* was essentially negative except for a trace of albumin; specific gravity, 1.010. *Feces* examination was negative for parasites and ova; occult blood was present.

Roentgen ray examination (10-22-42) showed an extensive infiltration of both lungs, miliary in type. Diagnosis: pulmonary tuberculosis, miliary. Re-examination showed the same picture on 10-24-42.

Clinical Course. During the 1st week of hospitalization, the patient had recurring chills every evening with rise of temperature to 104° F., followed in 7 hours by a drenching sweat. The 2nd week the evening temperature only spiked to 102° F., with the chills and sweats as before. The distention of the abdomen was very difficult to control for the 1st week, after which the patient was somewhat more comfortable. The cough and blood-streaked sputum persisted; the dyspnea became progressively worse. The lung findings changed gradually each day until 6 days before death, at which time the percussion note was flat throughout. Breath sounds were barely audible, and no râles were present. The pulse rate became very irregular as a result of numerous premature contractions and was almost imperceptible during the last 6 days. Terminally, the respiratory rate rose to 40 per minute. Restlessness and dyspnea were marked. Coma and death occurred on the 13th hospital day.

Postmortem Examination (15 hours after death). The body was that of a negro male, 23 years of age, fairly well developed, but emaciated, measuring 64.5 inches in length, and weighing approximately 90 pounds. The head showed nothing of significance other than poor oral hygiene and slight oozing of bloody fluid from the nose. A few small lymph nodes were found in the left axilla. The omentum was adherent to an enlarged spleen. The peritoneum was smooth otherwise, and there was 100 cc. of clear yellow ascitic fluid. Both lungs filled their respective pleural cavities. There were tough fibrous adhesions posteriorly on both sides, as well as on the diaphragmatic surface and apex of the right lung. All lung fissures were virtually obliterated with adhesions. There was a small amount of cloudy fluid in each pleural cavity and a rather diffuse recent fibrinous reaction. The pericardial sac was thin and contained a small amount of clear yellow fluid. The heart was approximately normal in size.

The left and right *lungs* weighed 1080 and 1130 gm. respectively. Both pleural surfaces were roughened by numerous fibrous and fibrinous adhesions. All lobes were very firm and presented many areas of increased density.

Crepitus was markedly reduced. The cut surfaces of all lobes were similar. They were firm, dirty yellowish gray, with a few small scattered areas of red, relatively normal lung. One 2 x 3 cm. area in the subapical portion of the right upper lobe showed markedly increased density. Fibrosis was generally increased throughout, but no calcium was encountered. The hilar lymph nodes were not prominent. There was no cavitation.

The *heart* weighed 300 gm. and presented nothing of note grossly.

The *spleen* weighed 650 gm. The external surface was grayish red and presented shaggy fibrous tags over its upper portion. The pulp was exceptionally firm and light red. It was scraped with difficulty; the normal architecture was obliterated.

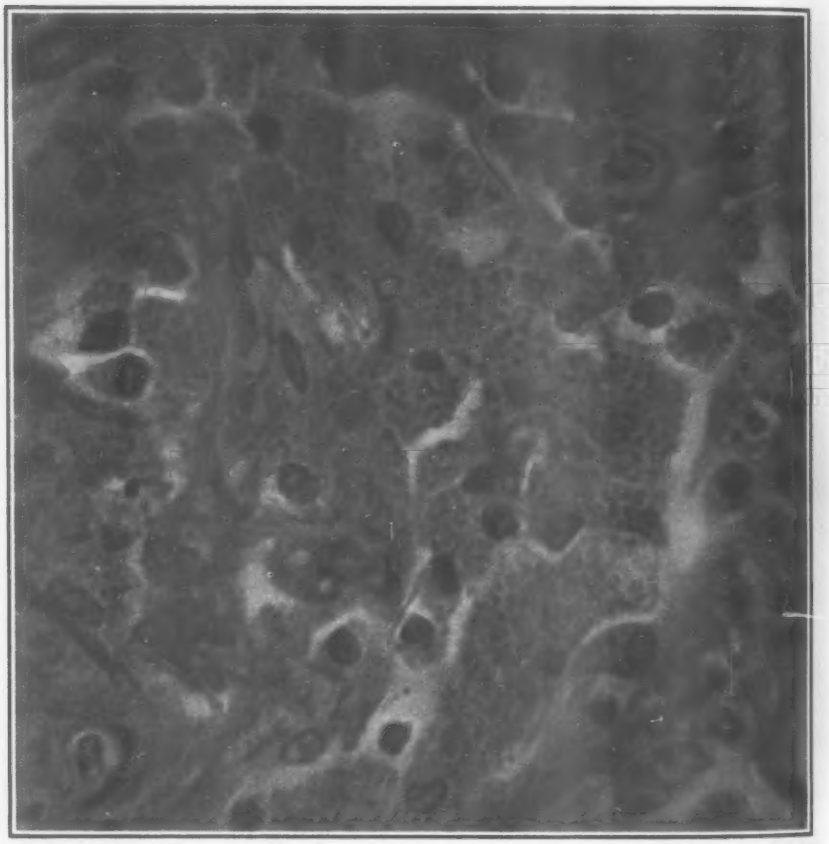

FIG. 1. *Lung* (440 ×): Pulmonary alveoli filled with parasite-laden macrophages. Fibroblastic activity is also evident.

The *liver* weighed 2040 gm. Its external surface was smooth and presented numerous small, firm, circumscribed, grayish white areas varying in size from 1 to 2 mm. These areas were not calcified. The cut surface showed little of note other than an occasional small rounded area such as presented on the external surface.

The *gall bladder*, *biliary duct system*, *adrenals*, and *gastro-intestinal tract* showed nothing of note. The *pancreas* weighed 60 gm. and revealed no gross findings.

The *peripancreatic* and *portal lymph nodes* were enlarged, varying from 1 to

2.5 cm. in diameter. They were firm and presented a homogeneous yellowish gray cut surface.

The left and right *kidneys* weighed 210 and 195 gm. respectively. Their capsules were thin, but stripped with some difficulty, revealing a granular reddish brown cortical surface. Consistency was moderately increased, but the cut surface presented normal markings.

Microscopic Examination. Lungs: The primary lesion appears to be a nodular area of consolidation resulting from numerous large parasite-laden macrophages filling the alveolar spaces. The parasites are round to ovoid encapsulated structures about one-third to half the size of a red cell and present a central Gram-positive polar staining ovoid "nucleus." The nodular

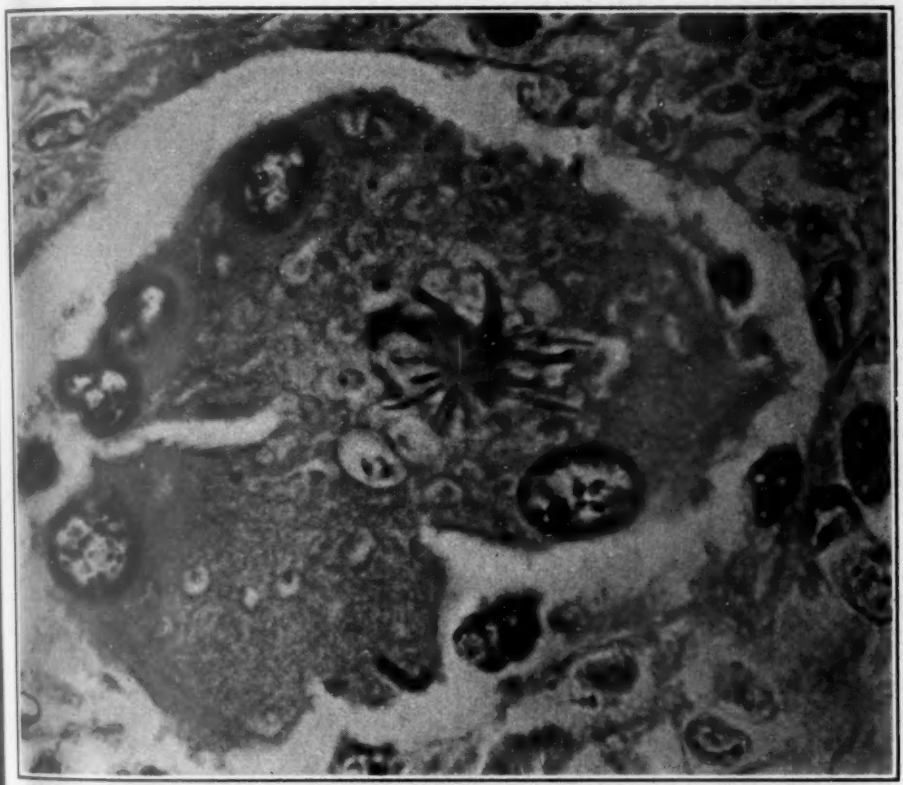

FIG. 2.—*Spleen* (950 ×—oil immersion): "Asteroid" inclusion forms in Langhans' giant cells.

areas exhibit a marked tendency towards confluence. The larger lesions thus formed have large zones of central necrosis which still retain the "ghost-like" architecture of the lung structure. The pulmonary vessels at these sites exhibit a rather marked obliterative endarteritic process which would appear to have contributed to the necrosis. Surrounding the necrotic areas there is a rather marked proliferation of fibroblasts obliterating the air spaces and enclosing myriads of parasite-laden macrophages. In such granulomatous areas numbers of necrotic neutrophils can frequently be found. Surrounding the nodules the lung parenchyma exhibits complemental emphysema and mild fibrous septal thickening. In some sections, presumably from the subapical area, there are small wedge-shaped areas of dense subpleural scarring resemb-

ling the common subapical scars described in association with a healed reinfection type of tuberculosis. There is a moderate degree of parenchymal fibrosis too, which appears to be entirely independent of the principal process already described. However, the scarred areas accentuate the dilated lymphatic vessels which contain numerous and often parasite-laden macrophages (Fig. 1).

Liver: Principally in the subcapsular area, but also involving many of the portal spaces, there are variably-sized granulomatous nodules which compress and distort the adjacent liver parenchyma. The nodules contain frequent parasite-laden macrophages and are mildly infiltrated with round cells. The remaining bulk of the liver tissue preserves its normal lobulation which is accentuated by moderate sinusoidal dilation and congestion. The Kupffer cells are hypertrophied and often contain numbers of organisms.

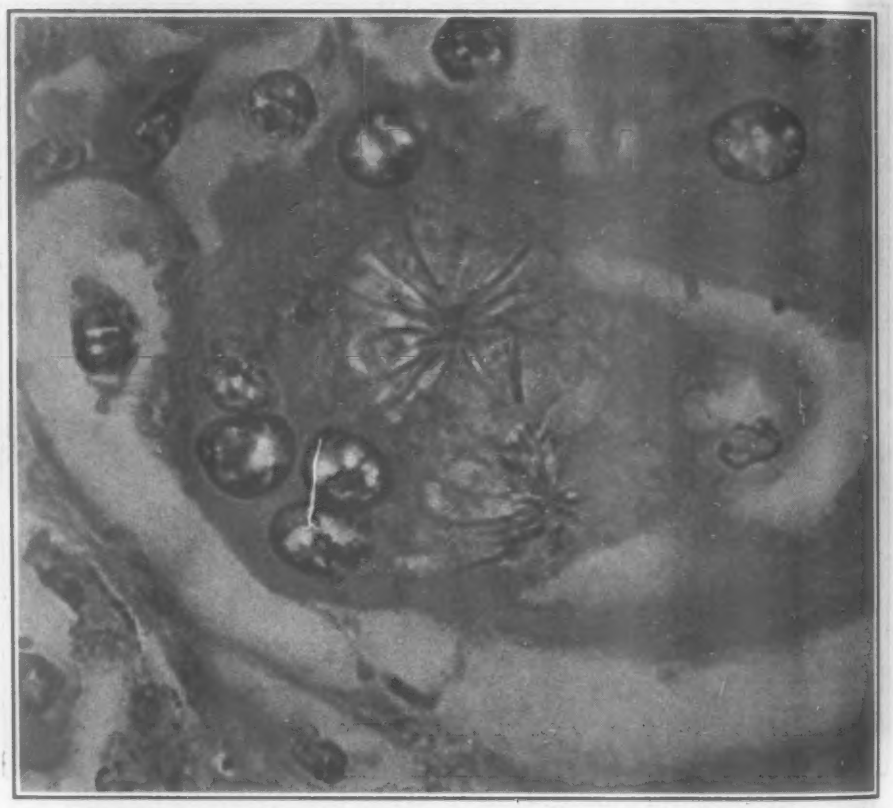

FIG. 3.—*Spleen* (950 ×—oil immersion): "Asteroid" inclusion forms in Langhans' giant cells.

Spleen: There is a marked alteration of the splenic architecture by marked fibrosis along the vascular tree and trabecular framework. The broad bands of fibrous tissue thus formed are featured by the presence of numbers of large Langhans' type giant cells. Lymphoid follicles are largely obliterated. The pulp persists as islets of sinusoids between large fibrous bands. Although organisms may be demonstrated in macrophages present in the sinusoids, they are comparatively few in number. The Langhans'-giant cells often contain one or more prominent amphophilic and Gram-positive stellate or "asteroid bodies," which are contained in a scalloped, irregular vacuolar space. The appearance resembles a flower whose petals are formed by clusters of what

appear to be clear ovoid bodies and whose central portion is amphophilic. Radially arranged, slightly tortuous bands of similar staining reaction appear to be dispersed amongst the ovoid bodies. However, selected asteroid bodies clearly show the presence of an unstained capsule covering each arm. It may be that their overlapping produces the effect of clustered ovoid bodies, but in many instances such clusters can be demonstrated in the absence of an asteroid. These ovoid bodies have amphophilic "nuclei" and resemble the organisms seen in other tissues. However, they frequently fail to retain the Gram stain (Figs. 2 and 3).

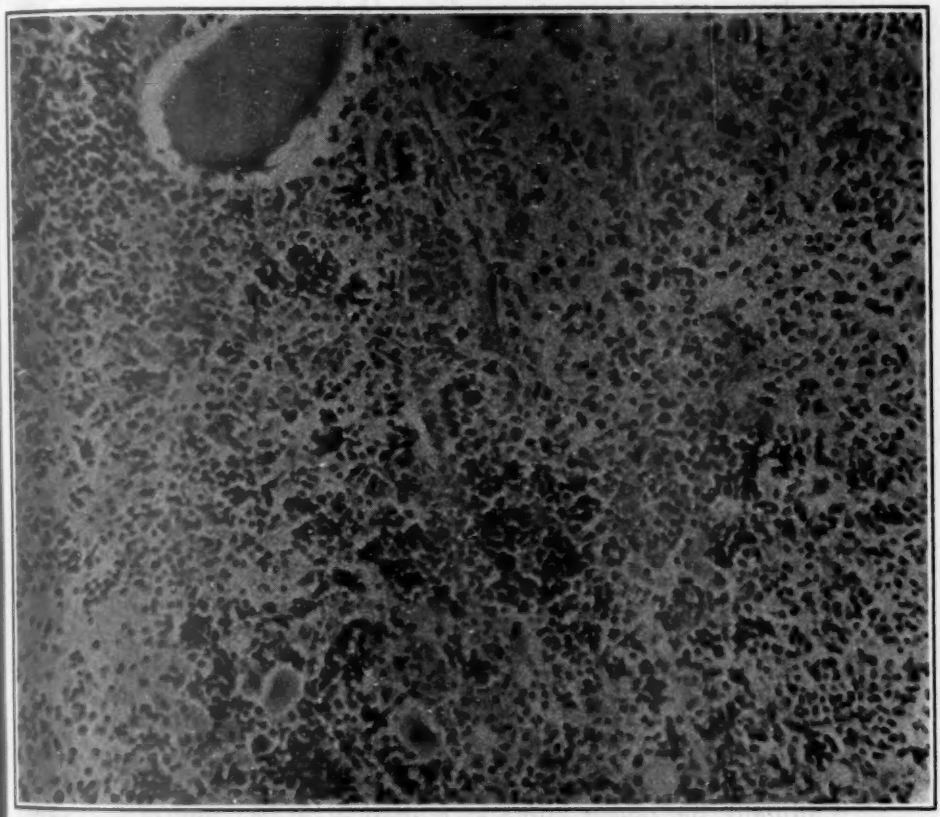

FIG. 4.—*Bone marrow* (440 ×): Granulomatous foci displace and encroach upon the functional hematopoietic marrow which presents as a wedge in the center of the field. Anemia and leukopenia are thereby explicable on a myelophthisic basis.

Lymph Nodes: There is a marked alteration of the nodal architecture by an enormous hypertrophy of the reticulo-endothelial cells and by fibrosis and hyalinization of the lymphoid cords. Numerous cells of the macrophage variety fill and distend the sinusoids often forming nodular clusters. Numbers of ovoid intracellular organisms, as previously described, may be demonstrated.

Kidneys: Intertubular round and plasma cell infiltrates are prominent. The renal tubules are moderately separated by the interstitial infiltration and edema and exhibit rather marked parenchymatous degeneration.

Pancreas and *skeletal muscle:* Not noteworthy.

Heart: There is a mild rather patchy increase of mononuclear cells in the interstitial stroma. The muscle fibers are of average size with clearly defined striations.

Bone marrow: Sections of the rib marrow show numerous granulomatous foci which largely displace a qualitatively hyperactive hematopoietic tissue. Numbers of organism-laden macrophages may be demonstrated in the granulomas. It is quite evident that there is a very marked quantitative decrease of the functioning blood-forming tissues (Fig. 4).

Miscellaneous: Occasional giant cells of the Langhans' variety may be demonstrated in granulomatous areas of the lung, liver, lymph node, and bone marrow, as well as in the spleen as described above. "Asteroid forms" can be demonstrated in the giant cells at any of these sites.

Comment. The publication of over 30 cases since 1938 when only 7 cases were reported prior to that time would indicate that histoplasmosis, although not common, is perhaps not as rare as was once thought. Histoplasmosis may be suspected when a patient presents continued fever, leukopenia, splenomegaly, hepatomegaly, anemia, lymphadenopathy, skin lesions, and gastro-intestinal ulcerations. Clinically the last three features were not present in the case reported herein. Obviously the more common diseases must be ruled out before considering the rareties. In the present case the clinical picture was confused by a Roentgen ray diagnosis of miliary tuberculosis, with which the finding of 9 sputa negative for acid-fast organisms was not incompatible. Hindsight, in the present case, would indicate that the fungus was probably present in the sputum, and if suspected, could have been demonstrated by smear or culture. Again, more careful blood studies, cultures, or bone marrow examinations could have led to an antemortem diagnosis as made in some of the previously reported cases. Biopsy of enlarged lymph nodes or of granulomatous skin, nasopharyngeal, or gastro-intestinal lesions constitutes the remainder of the diagnostic armamentarium.

The presence of anemia and leukopenia in histoplasmosis may be beautifully explained by the bone marrow findings in the present case as a quantitative reduction of the hematopoietic marrow by multiple granulomatous lesions which displace it. This appears to be primarily a myelophthisic anemia, although secondary toxic effects cannot be ruled out. The presence of rather marked marrow hyperplasia between the granulomatous foci would speak against any marked toxic effect of the systemic infection.

Culturally the fungus grows as a yeast at 37° C. and produces mycelia with aerial hyphæ at room temperature. Experimentally, both forms are pathogenic, but the mycelial form reverts back to the yeast form in tissues (Parsons).

"Asteroid forms" described in Langhans' giant cells in this case were previously described by Wolbach (1911). This author presented 5 cases wherein these cell inclusions were found. They were associated with disseminated granulomatous lesions of various sorts and involved lymph nodes in 3 cases; the lungs in 3 cases; and the spleen and liver in 2 cases. The primary pathologic diagnoses were diverse, and in all cases specific granulomata were carefully ruled out. For this reason the inclusions were not regarded as specific for any disease.* The

* Dr. Melvin Friedman, in our department, has recently observed a case not associated with histoplasmosis, where asteroid forms were so numerous that a detailed schema of their development could be constructed.—EDITOR.

staining reactions led Wolbach to hypothesize that these forms "are produced by etching of the fibrin reticulum which for some reason or other has acted as a foreign body, and has been taken up by endothelial leucocytes."

Summary. 1. A case of histoplasmosis occurring in a negro soldier from Alabama is reported.

2. The diagnosis was made by postmortem examination after a clinical diagnosis of miliary tuberculosis was made.

3. At the postmortem table a diffuse form of tuberculous pneumonia was suspected, and the correct diagnosis was not made until the microscopic sections were read.

4. Encapsulated "asteroid forms" are described in the granulomatous foci.

5. An explanation for the occurrence of anemia and leukopenia in this case is given.

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HEPATORENAL FAILURE IN THE WATERHOUSE–FRIDERICHSEN SYNDROME*

Clinico-Pathologic Observations in Two Cases With Prolonged Survival Periods

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The literature on the Waterhouse-Friderichsen syndrome has repeatedly stressed the concept of a distinct clinical entity characterized by an acute fulminating meningococcemia with adrenal hemorrhages and a rapidly fatal termination. A striking feature of this syndrome is the brevity of the clinical course, the majority of cases succumbing within 24 hours or less.[1,4,5,7,8,10–12,16–18,20,21] Levinson,[13] Lindsay, Rice, Selinger, and Robins,[14] Drummond and Tooke[6] have reported cases which have lived for periods as long as 48 hours but there are no reports in the literature of cases which survived beyond this time. Investigators unanimously report an invariably fatal outcome in the Waterhouse-Friderichsen syndrome with the single exception of Carey[3] who claimed a recovery.

This syndrome affects children primarily, 70% of the reported cases

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occurring under 2 years of age. Its rarity in adults has been emphasized by Aegerter,[1] who, in a review of the literature, found only 6 adult cases.

The paucity of clinical studies in this syndrome is due to the fulminating and fatal course so characteristic of these cases, which precludes any extended bedside observations. However, in the treatment of 134 cases of meningococcic infections by the authors[15] at the Station Hospital, Fort McClellan, Alabama, 5 cases of the Waterhouse-Friderichsen syndrome were encountered, of which 2 were unique because of their prolonged clinical courses. This paper is a presentation of hitherto unreported clinico-pathologic features observed by us in these 2 protracted cases. Our experience indicates that the cases of the Waterhouse-Friderichsen syndrome which survive the initial shock will succumb in a state of renal insufficiency directly attributable to severe hepatic necrosis. This combination of clinical and pathologic factors has been described as the hepatorenal syndrome or hepatorenal failure. Briefly, the hepatorenal syndrome is a process which terminates in death with uremic symptoms in its final phase clinically, and in which at necropsy, hepatic as well as renal damage is demonstrable.

The hepatorenal syndrome was first described by Heyd in 1923 to explain certain deaths following operative procedures on the external biliary system.[9] Since that time a voluminous literature has accumulated which has been excellently summarized by Boyce.[2] In a recent review of the literature, Reich[19] called attention to the occurrence of the hepatorenal syndrome in many diverse medical and surgical conditions, such as diphtheria, Addison's disease, toxemias of pregnancy, intestinal obstruction, biliary tract diseases and burns. Wilensky and Colp[22] have advanced the most satisfactory theory thus far to explain the hepatorenal syndrome. They postulate the existence of an initial lesion which affects the hepatic cells primarily and the renal nephron secondarily.

Case Reports. Case 1. A. J. W., a 20 year old male, was admitted to the hospital on Jan. 24, 1943, complaining of a sore throat, cough, chills and fever. He denied any muscle pains, vomiting or headache. On admission, the physical examination was entirely negative except for a moderately inflamed pharynx. No nuchal rigidity was present and petechiæ were not observed. Temperature on admission was 102.8° F., pulse 90 and respirations 20. The diagnosis of an upper respiratory infection was made and symptomatic therapy instituted. His temperature fluctuated between 99° and 103° F. for the first 3 days and then gradually fell to normal on the 5th day. He remained afebrile until the evening of the 7th day when his temperature rose to 101.6° F. and he appeared acutely ill. His symptoms now were malaise, chilly sensations, headache and weakness, but no abnormal findings were noted on examination. A blood count showed 11,150 white blood cells. On the 8th day, the patient presented a dramatic change. He was desperately ill, pallid, apprehensive, restless and in severe shock. The sensorium was clear and the patient was well oriented. There were numerous petechiæ and purpuric lesions distributed over the entire body. Facial edema was observed particularly about the eyes. The pharynx was red and injected. Nuchal rigidity was absent and no abnormal neurologic reflexes were elicited. The temperature was 96° F., pulse imperceptible, respirations 28, and the blood pressure was unobtainable. A second blood count revealed 47,250 white blood cells with 94% polymorpho-

nuclears. Lumbar puncture was not done at this time due to the patient's critical condition.

A diagnosis of an overwhelming meningococcemia with adrenal hemorrhages (Waterhouse-Friderichsen syndrome) was made. The patient was placed in the antishock position and an infusion of 1500 cc. of 5% glucose in normal saline was given intravenously to which 30,000 units of meningococcus antitoxin were added. Following this infusion, the blood pressure rose to 60/40 and the pulse was 130 and of fair quality. One hour later, a 5% sodium sulfadiazine solution was given intravenously (5.5 gm. in 111 cc. of sterile distilled water). The blood sulfadiazine concentration 20 minutes later was 15.5 mg. per 100 cc. Massive oral doses of sulfadiazine were administered according to the following schedule: initial dose, 8 gm.; second dose 2 hours later, 5 gm.; third dose 3 hours later, 4 gm.; fourth dose 4 hours later, 4 gm.; and 3 gm. every 4 hours for the next 3 doses. Thereafter dosage was regulated to maintain the blood concentration between 15 and 20 mg. On this régime the patient appeared to rally. A total of 80,000 units of meningococcus antitoxin was given intravenously within the first 18 hours of therapy. To combat the shock and impaired peripheral circulation, 500 cc. of blood plasma was given. The blood pressure rose to 80/60. Adequate amounts of fluid and periodic injections of desoxycorticosterone intramuscularly were administered.

At the onset of treatment and throughout the patient's course, there was a marked disturbance of renal function which was characterized by complete anuria for the first 24 hours followed by oliguria persisting until death. The specimens of urine obtained revealed no abnormal changes. In addition, the patient was incontinent of feces and passed many brown liquid stools until he succumbed.

On the 9th hospital day, the patient was still conscious and oriented but the respirations were rapid, labored, and shallow. Cyanosis was absent. Many bubbling râles were heard over the entire chest. The edema of the face persisted, but was not found in any other part of the body. The blood pressure remained at 80/60. The temperature was 98.4° F., pulse 110 and respirations 36. The blood sulfadiazine level was 14.4 mg. per 100 cc. On lumbar puncture, a crystal clear spinal fluid under normal pressure was obtained which was negative on examination. Colonies of *Neisseria intracellularis* Type II-IIa were grown from the blood culture. An additional 500 cc. of plasma was given. Because of dyspnea, the patient was placed in an oxygen tent.

On the 10th hospital day, the patient became stuporous but responded to painful stimuli. Bubbling râles were still audible. Temperature was 98° F., pulse 90 and respirations 40. Blood pressure was maintained at 80/60. Blood sulfadiazine concentration was reported as 19.5 mg. The non-protein nitrogen was 86. Despite all therapy, the course of the disease continued unfavorably, and the patient succumbed on the 11th hospital day, 80 hours after the onset of the Waterhouse-Friderichsen syndrome.

Autopsy. The body was that of a well-developed, thin young man. A moderate number of petechiæ were scattered over the body. Four hundred cc. of a clear, straw-colored fluid was present in each pleural cavity and 1000 cc. of a similar fluid in the abdominal cavity. This fluid clotted spontaneously during the course of the autopsy. The heart was enlarged and the right auricle was dilated. The liver weighed 2035 gm. and, on section, revealed moderate congestion. The kidneys appeared normal, the right weighing 185 gm. and the left 170 gm. The capsule stripped with ease, revealing a smooth, red-brown surface. The cortico-medullary demarcations were distinct. No exudate was present in the brain and the ventricles contained clear cerebrospinal fluid. The most striking finding was noted in the adrenal glands, which weighed 15 gm. together. Both adrenals were firm and in normal position but showed hemorrhagic areas involving the left more than the right.

Microscopic examination showed histologic changes in the adrenals, liver and kidney. The adrenals showed hemorrhages of varying sizes involving both the cortical and medullary areas. The general architecture of the liver was normal. There was central vein and sinusoidal engorgement. In the

central zone, there was marked dissociation of liver cords, many of the cells showed necrobiosis and many were heavily laden with bile pigment. The mid-zone showed necrobiosis and vacuolization. The liver cells in the peripheral zone showed no noteworthy change. In the portal areas there was a moderately intense diffuse polymorphonuclear and lymphocytic infiltration with mild edema. The kidney showed increased cellularity and avascularity of the glomerular tufts. Focal areas of polymorphonuclear infiltration and edema interstitially were observed. There was cloudy swelling of the convoluted tubular epithelium and albuminous deposits were present in the tubular lumina.

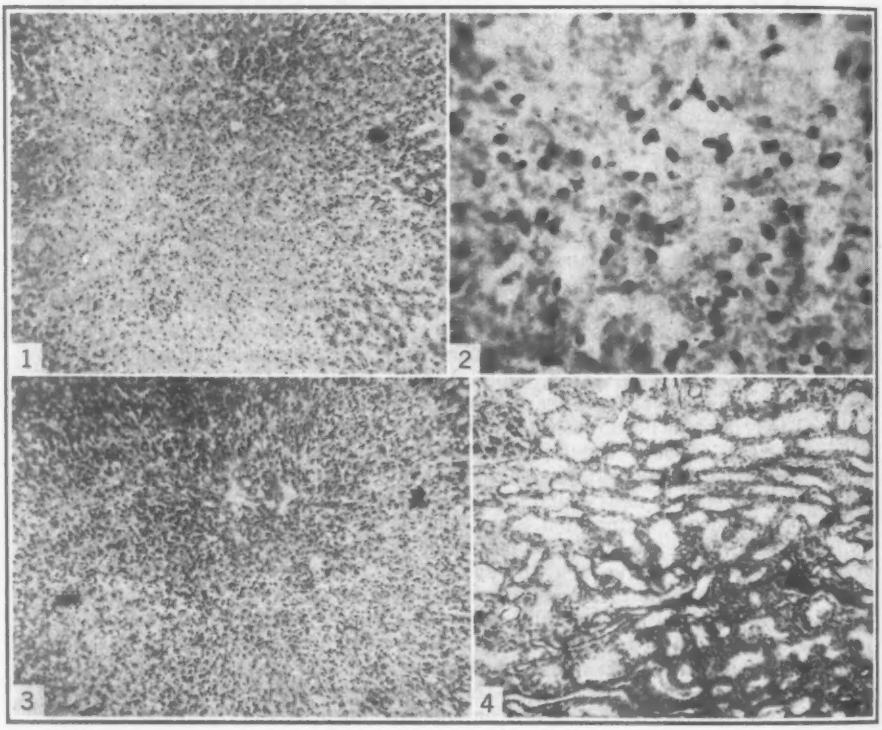

FIG. 1.—Case 1. Low-power photomicrograph of the liver demonstrating far-advanced central necrosis. × 100.

FIG. 2.—Case 1. High-power photomicrograph of the liver showing cellular necrosis with polymorphonuclear infiltration. × 440.

FIG. 3.—Case 2. Low-power photomicrograph of the liver showing liver cell necrosis with fatty metamorphosis in the peripheral zone. × 100.

FIG. 4.—Case 2. Low-power photomicrograph of the kidney showing increased cellularity and avascularity of the glomerular tufts. Albuminous casts are present in the lumina of the tubules. × 440.

Comment. The outstanding feature of this case is the long clinical course of 80 hours in a syndrome which ordinarily terminates in 24 hours or less. Unfortunately, no sodium, potassium and chloride determinations were obtained. Although clinically, the evidence suggested renal failure, the picture was dominated pathologically by liver necrosis (Figs. 1 and 2).

CASE 2. C. W., a 20 year old obese white male, was admitted to the hospital on Feb. 17, 1943, complaining of chills, fever, headache, and generalized muscular pains of 24 hours duration. He was seriously ill but rational and oriented. The physical examination disclosed facial edema with puffiness about the eyes. The body was covered with numerous petechial and purpuric areas. No nuchal rigidity was present. The Kernig and Brudzinski signs were absent. The spleen was not palpable. The temperature was 98.8° F., pulse 100, respirations 22, and the blood pressure 60/40. No lumbar puncture was performed due to the poor condition of the patient. A blood count revealed 66,950 white blood cells with 96% polymorphonuclears. The red cell count was 5,510,000 with a hemoglobin of 13.8 gm. A blood culture was positive for the *Neisseria intracellularis* Type I. A diagnosis of a fulminating meningococcemia with adrenal hemorrhages (Waterhouse-Friderichsen syndrome) was made.

The patient was immediately given 5.5 gm. of sodium sulfadiazine intravenously in a 5% solution of sterile distilled water. Within the first 12 hours of admission, he received a total of 80,000 units of meningococcus antitoxin intravenously. Adequate fluids were administered both orally and intravenously and 50 cc. of adrenal cortical hormone were given by the latter route daily throughout the course of the disease. Massive doses of sulfadiazine were given orally, the initial dose 8 gm. The total dose for the 1st day of therapy was 29 gm. Twenty-two hours after hospitalization, the patient received 500 cc. of plasma. The blood pressure rose to a level of 80/60. The initial blood sulfadiazine concentration 14 hours after admission was 2.5 mg.

Complete urinary suppression was observed during the first 24 hours of hospitalization. At this time the patient was catheterized and 2 ounces of cloudy, amber urine obtained. On examination, the urine was negative except for 2+ albumin. Diarrhea was a persistent complaint throughout his course. The stools were liquid, light brown in color but not bloody. No abdominal pain was present.

On the 2nd hospital day, the patient appeared restless and apprehensive but the sensorium was clear. Facial edema persisted. Temperature was 97.2° F., pulse 130, respirations 28 and the blood pressure 100/80. The patient voided 3 ounces of urine spontaneously which showed a specific gravity of 1.025 and 1+ albumin. Microscopically, a few granular and cellular casts were found with 50 to 60 red blood cells per high-power field. A blood count was 20,300 white blood cells with 95% polymorphonuclears. The non-protein nitrogen was 52 and the blood sulfadiazine level 10.2 mg. Efforts to combat the impaired renal function with hypertonic glucose, aminophylline, hot colonics, and coffee were unsuccessful.

On the 3rd hospital day, the patient was definitely worse, although still conscious and oriented. His respirations were rapid and shallow, averaging 54 per minute. Slight cyanosis was evident for the first time. Numerous new petechial and purpuric areas appeared and several older lesions showed necrotic changes. Temperature was 97.2° F., and pulse 130. The blood count was now 35,750 white blood cells with 98% polymorphonuclears. A blood sulfadiazine concentration reached a level of 11.7 mg. The non-protein nitrogen continued to rise, reaching 91 mg. per 100 cc., and the creatinin 7 mg. per 100 cc. A specimen of catheterized urine (1 ounce) showed 2+ albumin, 5 to 6 red blood cells, 1 to 2 hyaline casts, and a few cellular and granular casts. The patient was placed in an oxygen tent, because of cyanosis and dyspnea.

On the 4th hospital day, the patient lapsed into stupor and was aroused with difficulty. Weakness and cyanosis were more pronounced and air-hunger more marked. Temperature was 98° F., pulse 140, respirations 52, and the blood pressure 120/80. The blood count revealed 49,450 white blood cells with 93% polymorphonuclears. The red cell count was 4,900,000 with 11.2 gm. of hemoglobin. The blood sulfadiazine level reached 26.1 mg. The non-protein nitrogen rose to 96.9 mg. per 100 cc. and creatinin to 7.4 mg. The blood chlorides were 412.5 mg. per 100 cc.

The patient's course progressed rapidly downhill and he succumbed on Feb. 21, 1943, 88 hours following admission to the hospital.

Autopsy. The body was that of a well-developed, obese young man. The skin was covered with many petechial and purpuric areas, some of which showed early necrotic changes. A moderate amount of clear, straw-colored fluid (500 cc.) was present in the serous cavities. The heart was enlarged and weighed 590 gm. The right auricle showed great dilatation. The liver weighed 2790 gm. and on section showed moderate congestion. The kidneys were large and felt less firm than usual. The right kidney weighed 240 gm. and the left 280 gm. The capsule stripped with ease. On section, the kidneys showed considerable congestion. The cortico-medullary demarcations were indistinct. The brain revealed marked engorgement of its superficial vessels but no gross exudate was seen. The ventricular fluid was clear. The adrenals were hemorrhagic and on section, numerous small hemorrhages were noted involving both the medulla and cortex.

On microscopic examination, significant histologic changes were found in the adrenals, liver and kidney. The adrenals showed numerous small hemorrhages involving both medulla and cortex. The architecture of the liver lobules showed marked destructive changes in the central and mid-zones. The liver cords in these zones were completely destroyed. The cells were only occasionally recognizable and moderate bile pigmentation was present. Numerous areas of hemorrhage and polymorphonuclear infiltration were seen. In the peripheral zone, the liver cords were preserved, but the liver cells were swollen with marked vacuolization and granularity of their cytoplasm. Fatty metamorphosis was a prominent pathologic feature. The Kupffer cells were not noteworthy. The central veins and sinusoids were engorged and the portal areas frequently showed a moderate polymorphonuclear infiltration with small nests of lymphocytes. The kidney architecture was preserved. The glomeruli were normal except for albuminous deposits in the capsular spaces and marked cellularity with avascularity of the tufts. The epithelial cells of the proximal convoluted tubules showed cloudy swelling and had a "ground glass" appearance. Albuminous casts were plentiful.

Comment. This case is another illustration of severe meningococcemia with marked adrenal hemorrhages associated with a prolonged survival period. The clinical course and mode of death is strikingly similar to that of Case 1. Paradoxically, a sole blood chloride determination a few hours prior to death was found to be within normal range. The question is raised, therefore, as to whether the electrolyte balance is disturbed in the Waterhouse-Friderichsen syndrome. The entire clinical picture was overshadowed by impaired renal function but at necropsy, liver necrosis was an impressive feature (Fig. 3). This case is unique in that the patient survived for the amazingly long period of 88 hours despite such extensive adrenal destruction.

Discussion. The 2 cases of the Waterhouse-Friderichsen syndrome described in this paper were unusual because of their relatively prolonged survival periods, 80 and 88 hours respectively, and the similarity of their clinico-pathologic findings. The fulminating character of this syndrome has made impossible any detailed observations heretofore, and this appears to be the first report to describe hepatorenal failure in protracted cases of the Waterhouse-Friderichsen syndrome.

The salient clinical features of both cases were so similar as to warrant detailed discussion. The onset of the acute phase of the disease was marked by severe shock and pallor. Consciousness and orientation were maintained until shortly before death. Facial edema, particularly about the eyes, was remarkable in its similarity to that

of nephritis. Edema involving other portions of the body could not be demonstrated clinically. Interestingly enough, subnormal temperatures persisted throughout the course of the infection in spite of a severe overwhelming septicemia, and recovery from the initial shock as evidenced by a return of the blood pressure to normal or quasi-normal levels. No agonal rise in temperature occurred. Diarrhea was present from the onset and persisted throughout the course of the disease. The stools were liquid and tan in color but not grossly bloody. Jaundice or other clinical evidences of hepatic dysfunction were absent.

The striking and unusual clinical feature was the initial anuria followed by a severe oliguria which was associated with progressive impairment of renal function. This observation was noted throughout the clinical course of both patients. Although the non-protein nitrogen and creatinin rose steadily, there were no clinical manifestations of uremia.

It is important to mention at this point, our 3 other cases of the Waterhouse-Friderichsen syndrome not reported in this paper. Two of these cases had fulminating clinical courses terminating within 24 hours. At necropsy, the pertinent findings were severe hemorrhages and destruction of the adrenal glands coupled with a mild hepatitis limited to the central zones. However, no noteworthy renal changes were demonstrable. The third case survived 40 hours. In this case, hepatorenal failure was demonstrated early. The blood chemistry findings 16 hours after admission revealed a non-protein nitrogen of 46 mg. per 100 cc., creatinin 5.8 mg., and chlorides 454 mg. Thirty-six hours after admission the non-protein nitrogen rose to 67 mg. per 100 cc., creatinin 9 mg., and chlorides 470 mg. An icteric index at this time was 13.7.

On the other hand, the 2 cases of the Waterhouse-Friderichsen syndrome with prolonged clinical courses, died in a state of renal insufficiency, and showed at necropsy, moderate adrenal hemorrhages with severe hepatitis. In addition, the kidneys revealed glomerular and tubular changes and the pathologic features of both were similar but differed only in degree of severity (Fig. 4).

Case 2 demonstrated a more advanced stage of hepatic destruction than Case 1. Histologically, the noteworthy feature was severe necrobiosis of the liver cells, but whereas in Case 1 the central and mid-zones only were involved (Fig. 1), in Case 2 the central, middle and peripheral zones showed these extensive destructive changes (Fig. 3). The histologic findings in the kidneys of both cases were comparable but again differed in degree of severity. Both cases showed increased cellularity and avascularity of the glomerular tufts. Similarly, cloudy swelling of the convoluted tubular epithelium and albuminous deposits in the lumina were present but more marked in Case 2 (Fig. 4). These findings were essentially in agreement with those described by Wilensky[23] in the hepatorenal syndrome. From the above facts, life expectancy appears to be inversely proportional to the extent of adrenal hemorrhage; that is, the greater the adrenal hemorrhage, the shorter

the clinical course and the less likelihood for the development of hepatic destruction.

It seems logical to conclude from a correlation of the clinico-pathologic evidence in our cases that 2 clinical stages exist in the Waterhouse-Friderichsen syndrome. The first or fulminating stage is generally recognized and consists of severe shock with circulatory collapse. Survival of this stage ushers in the hitherto undescribed second or hepatorenal stage which is characterized clinically by marked oliguria with azotemia and pathologically by severe toxic hepatitis associated with glomerular and degenerative tubular changes.

The problem of why hepatorenal failure occurred only in the cases of the Waterhouse-Friderichsen syndrome and not in uncomplicated meningococcemias, cannot be ignored. Infection alone fails to explain satisfactorily this puzzling fact and our experience has shown that the hepatorenal syndrome does not occur in meningococcemia without adrenal involvement. It must be concluded that adrenal hemorrhage is a predisposing factor in the development of hepatorenal failure in the Waterhouse-Friderichsen syndrome. After evaluating the existing theories on the hepatorenal syndrome, coupled with an analyses of our cases and stressing the important rôle played by the adrenals in detoxification and its close interrelationship with liver and kidney function, it seems reasonable to advance the following explanation for the mechanism producing hepatorenal failure in the Waterhouse-Friderichsen syndrome. Destruction of the adrenal glands by hemorrhage throws the full brunt of detoxification primarily upon the liver and secondarily, upon the kidneys, both of whose functions have been depressed from the onset by shock and toxemia. The partially disabled liver is so overwhelmed by toxins that it is unable to perform its physiologic detoxifying function. As a result, the liver undergoes toxic necrosis and a potent tissue toxin is elaborated which, together with the unneutralized bacterial toxins, flood the circulatory system. Finally, the kidneys attempt to rid the body of these harmful products of bacteria and deranged liver metabolism by excreting them through the proximal convoluted tubules. The renal tubules, in the performance of this function, undergo degenerative changes. In addition, glomerular changes of a nephritic type occur. The avascularity of the glomerular tufts is difficult to evaluate but we believe it is indicative of diminished renal blood flow. All these factors operating in unison plausibly explain the renal failure.

A fact worthy of consideration is that the toxins elaborated by the necrotic hepatic cells are harmful to the comparatively uninvolved normal tissue remaining in the liver. This was proven experimentally by Boyce[2] who reproduced similar pathologic changes in dogs by the intraperitoneal injection of water-soluble extracts of liver tissue from patients dying of the hepatorenal syndrome. The changes produced were lethal or sublethal depending upon the strength of the extracts employed.

In spite of the vigorous use of accepted methods of therapy, the out-

come of our cases was invariably fatal. The therapeutic measures employed may have contributed in prolonging the clinical course. However, when all factors are considered, it seems inconceivable that a patient can recover from the Waterhouse-Friderichsen syndrome. To support this contention is the unassailable evidence of severe crippling of hepatorenal function as has been pointed out and its utter incompatibility with life can hardly be questioned.

Summary. Two cases of the Waterhouse-Friderichsen syndrome with prolonged survival periods of 80 and 88 hours respectively and with death ascribed to hepatorenal failure are presented in detail. This appears to be the first such report in the literature. These cases are unique in that they are characterized clinically by renal failure and pathologically by hepatic necrosis and glomerular and tubular changes in the kidney. These findings are similar to those found in the hepatorenal syndrome.

In the light of our clinical observations, it is necessary to conclude that 2 stages exist in the Waterhouse-Friderichsen syndrome. The first stage is a fulminating one usually resulting in death from shock and toxemia. Survival of this period ushers in the second or hepatorenal stage wherein death ensues from hepatorenal failure.

The life expectancy in our cases was inversely proportional to the degree of adrenal tissue destroyed by hemorrhage.

Accepted modes of therapy administered to our patients may have prolonged the clinical course but did not alter the fatal outcome of the disease.

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OBSTRUCTIVE LESIONS OF THE MAIN RENAL ARTERY IN RELATION TO HYPERTENSION

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DURING the past decade a spotlight of considerable intensity has been focused upon the problem of experimental hypertension. A recent review of the present status of the relationship between human hypertension and that produced experimentally[30] indicates that although many questions pertaining to hypertension, as it occurs in human beings, have been clarified, others of a fundamental nature still remain obscure. There appears to be a widespread, tacit acceptance of the idea that an etiologic association exists between hypertension produced experimentally and that occurring in a great variety of pathologic lesions of the kidneys, notably those which affect the renal blood-vessels. Such an assumption implies that a similar mechanism acts to produce the hypertension in each instance. While the final proof of such a relationship must naturally rest upon an exact correlation of pathologic lesions with experimental methods, this is not always possible to make.

Diffuse sclerosis or constriction of intrarenal arteries has proved, up to the present time, to be technically impossible to produce in experimental animals as a means of initiating hypertension. Therefore, direct comparison cannot be made between experimental hypertension as produced by present methods and hypertension in man associated with chronic glomerulonephritis, chronic pyelonephritis or nephrosclerosis in all of which the vascular lesions occur in intrarenal arteries. On the other hand, lesions causing constriction of one or both main renal arteries closely simulate the experimental conditions of the arterial clamp used so successfully by Goldblatt,[11] Wilson and Byrom,[31] and others and provide probably the only human examples of hypertension in which the various factors can be accurately evaluated and in which a direct comparison with experimental procedures can be made. The present review comprises a critical survey of reported data bearing on the fundamental question of the rela-

tion of obstructive lesions of the main renal artery to hypertension in man. It is hoped that a clear understanding of the established facts pointing to a relationship between human and experimental hypertension will make the problem stand out in sharper relief and act in some measure as a guide to further investigations.

The literature of recent years contains a number of case reports and statistical surveys purporting to show that the "Goldblatt mechanism" is active in at least some cases of human hypertension, but despite the interpretations of most of the authors, such proof as does exist rests largely on circumstantial evidence. The elusive character of the problem depends, in the main, on the almost unavoidable failure to reproduce in any given human case all the steps required for a clear-cut, conclusive experiment.

It is natural that interest should have centered largely, but not exclusively, on examples of unilateral renal disease, reviewed recently by Abeshouse,[1] in which there is a possibility of removing the suspected cause of the hypertension by nephrectomy. This phase of the problem received an added impetus following the demonstration by Wilson and Byrom[31] that, in the rat, a variety of unilateral renal disturbances, including arterial constriction, would cause a persistent elevation of blood pressure. That man's reaction under these circumstances is probably more like that of the rat than of other experimental animals is indicated by the relatively few instances in which nephrectomy for a unilateral lesion constricting the main renal artery has successfully lowered the blood pressure from hypertensive levels. Unfortunately, the majority of reported cases have not been clarified until after death and, although much suggestive evidence has been derived from postmortem reconstruction, it is hoped that in the future more stress will be laid upon accurate diagnosis, early treatment and adequate follow-up studies.

Occlusive lesions of the renal arteries may be roughly divided into those which narrow the lumen from within and those in which the constriction is due to extrinsic factors. The available data will, therefore, be discussed under these 2 headings:

Narrowing Due to Intrinsic Factors. ARTERIOSCLEROTIC PLAQUES. An arteriosclerotic plaque, at or near the orifice of the vessel, would appear to be the commonest cause of unilateral or bilateral constriction of the renal artery, whether associated with hypertension or not. A number of individual cases of this type have been reported in the literature in which constriction of one or both main renal arteries by arteriosclerotic plaques has been assumed to bear an etiologic relationship to the hypertension which was present. In none of these is the evidence absolutely conclusive, although the vascular stenosis may have been a factor.

Freeman and Hartley[10] recorded the case of a 57 year old man whose right kidney was removed 2 years before death following traumatic rupture. Eight months before death his blood pressure was found to be 240/140, and at autopsy a large arteriosclerotic plaque was found narrowing the orifice of the left renal artery. The left kidney weighed 200 gm. and showed no arteriolar sclerosis, but there was some focal scarring and an interstitial inflammatory reaction. This case would appear to be a fairly clear-cut example of the Goldblatt mechanism; but there is a definite possibility of hypertension developing after nephrectomy in the absence of any such specific lesion, particularly in a man of this age.[5,14]

Another case of hypertension associated with a solitary kidney supplied by an obstructed renal artery in a man of 56 is that of Riggs and Satterthwaite.[25] The history indicated a sudden onset of severe hypertension

about 1 year before death, followed by rapid loss of vision 6 months later. Terminally the blood pressure was 260/140 and death occurred in uremia. Congenital absence of the left kidney, ureter and renal artery was discovered at autopsy, and the single remaining kidney showed marked sclerosis of intrarenal vessels, atrophy of glomeruli and tubules, and slight arteriolar necrosis. There was partial obstruction of the right renal artery due to a small, localized dissecting aneurysm and an arteriosclerotic plaque at the mouth of the vessel. In addition, the branches of the renal artery entered the kidney at a sharp angle. Any or all of the above disturbances could have caused renal ischemia, and the presence of marked vascular changes within the kidney is an added complication. This case illustrates some of the problems encountered in interpreting the relationship between hypertension and narrowing of the main renal artery.

In the case reported by Stewart[28], a 37 year old man with hypertension of less than 3 years duration who died from uremia with cardiac decompensation and anemia was found to have the orifices of both renal arteries surrounded and markedly stenosed by arteriosclerotic plaques. Both kidneys were considerably reduced in size, weighing 75 and 90 gm., and showed no arteriolar sclerosis but widespread destruction of parenchyma with fibrosis and lymphocytic infiltration. The changes were interpreted as the result of ischemic atrophy, and the view was supported by the fact that an aberrant artery apparently supplied additional blood to the least affected portions of each kidney. Although the author's interpretation of this case, that reduction in size of the orifices of the renal arteries resulted in a sufficient degree of ischemia to produce atrophy of the kidneys, is a tempting one, it is difficult, from the clinical and pathologic findings, to exclude some obscure intrarenal lesion as the initiating factor.

Finally such cases of arteriosclerotic occlusion of the main renal arteries associated with hypertension as those presented by Leiter (Case 2),[16] Saphir and Ballinger (Case 3),[27] and Tomlinson[29] hardly warrant inclusion in this review, since in each instance widespread changes in the renal parenchyma, sufficient in themselves to have caused the hypertension, were present in addition to the occlusive lesion in the renal arteries.

Seeing in these lesions a probable counterpart of the renal artery clamp used in the production of experimental hypertension, various investigators have endeavored to test the validity of the Goldblatt mechanism in humans by a statistical study of the occurrence of arteriosclerotic narrowing of the renal artery or arteries in large groups of autopsied cases of hypertensive and normotensive individuals.

One of the early references to renal arteriosclerosis as a possible factor in the production of hypertension was made by Moritz and Oldt.[21] These authors, in a study of arteriolar disease in a series of 100 hypertensive and 100 non-hypertensive individuals, found only "three cases of chronic hypertension in which there was no significant degree of renal arteriolar sclerosis." In all 3 cases arteriosclerosis of the main renal arteries was thought to be of sufficient severity to account for a decrease in the blood flow through the kidneys. Detailed descriptions of the vessels were not reported, however, and no mention was made of the state of the renal arteries in the other 97 hypertensive cases nor in the control group.

In 1939 Oppenheimer, Klemperer and Moschkowitz[22] reported 18 cases of unilateral renal artery constriction, presumably due to arteriosclerosis, from a series of 5000 consecutive autopsies performed at the Mount Sinai Hospital, New York City. Of this group 83% had hypertension, but in every instance there was evidence of definite intrarenal arterio- and

arteriolar sclerosis with arterial narrowing on the affected side which, at times, was even more marked than in the opposite kidney. From this finding and the associated severe arteriosclerosis of the aorta in these cases and controls with hypertension, it was concluded that the renal arterial constriction was an effect rather than a cause of the hypertension. Also in 1939 Blackman[2] found arteriosclerotic narrowing of one or both main renal arteries in 86% of 50 cases of essential hypertension as opposed to a comparable degree of arteriosclerosis and stenosis in only 10% of a control group of 50 non-hypertensive cases. Changes in the intrarenal arteries were present in every instance. There was a much lower incidence of acute arteriolar lesions in kidneys of which the main renal arteries were markedly narrowed. This suggests that the occlusive lesions exert a protective action on the blood-vessels of the affected kidneys in the terminal phase of the disease, but no light is thrown on the question of their etiologic relationship to the hypertension.

Essentially similar results have been more recently reported by Richardson.[24] In a series of 145 almost consecutive autopsies, 32 cases of essential hypertension were encountered. Of these, 25 showed the presence of arteriosclerotic plaques causing varying grades of stenosis of one or both main renal arteries. This finding contrasted sharply with that in 113 non-hypertensive controls where comparable lesions in the main renal arteries were seen in only 3 cases. As in the other series reviewed, arteriolar sclerosis was found in the kidneys of practically all the hypertensive group, irrespective of the presence or absence of stenosis of the main renal artery. Richardson attempted to reconcile this occurrence, with the constant absence of such intrarenal sclerosis in experimental hypertension due to clamping the renal arteries, by suggesting that any protective action occurs only in the late stages of the plaque development when stenosis is extreme, whereas blood pressure increases with the gradually increasing ischemia.

The results of the most recent study of the relationship between arteriosclerosis of the renal artery and hypertension, by Lisa, Eckstein and Solomon,[17] differ markedly from those of the authors already quoted. In 100 consecutive cases coming to autopsy in which blood pressure readings were available, hypertension was present in 56, while 44 were non-hypertensive. No appreciable difference in the average diameter of the renal arteries was found in the 2 groups, and in only 2 instances was there any marked stenosis due to arteriosclerotic plaques. Of interest also in this series was the large number of non-sclerotic renal vessels found in the hypertensive group. In 40% of these individuals, the vessels were regarded as normal while arteriosclerosis was absent in 56.8% of the non-hypertensives. Another significant finding was that little, if any, correlation could be demonstrated between the amount of sclerosis and the degree of constriction of the renal arteries.

Conclusions in the studies of Blackman[2] and Richardson[24] were based on similar methods of measuring the lumen of the renal arteries. This involved sectioning the vessels after fixation and estimating the degree of stenosis. In Blackman's report, actual measurements were made from stained microscopic sections. Lisa *et al.*, on the other hand made measurements of the arterial lumina in the unfixed state with graduated sounds and compared these with the size of the arteries measured according to Blackman's method. There was no constant relation between the size of the vessels when measured by these 2 methods and many non-sclerotic vessels with a good calibre in the unfixed state showed a considerable degree of narrowing after fixation and staining. On the basis of these

findings, it would seem that attempts to correlate the degree of narrowing of the lumen which existed during life with that observed in fixed, stained sections are of very questionable value.

From the above reports, it is apparent that atheromatous plaques in the renal arteries, usually associated with severe atherosclerosis in the aorta and elsewhere, occur in a high percentage of individuals with "essential" hypertension. However, critical analysis of the evidence would seem to favor the view that these lesions are secondary or incidental to the hypertension rather than causative in all but the few instances in which renal arteriolar sclerosis is absent.

EMBOLISM AND THROMBOSIS. The association of hypertension with partial or complete occlusion of the main renal arteries resulting from thrombosis or embolism has received relatively little attention in the past. However, a study of lesions of this type may well prove to be most fruitful in attempting to solve some of the still unanswered problems concerning the relationship between experimental and human hypertension.

It is often difficult, or even impossible, to ascertain definitely in this type of case whether the occlusion is due to embolism or thrombosis *in situ* so that the two will be considered together. The literature contains very few examples of thrombosis of the main renal artery associated with hypertension, and it is only within the past few years that hypertension and renal artery embolism with infarction have been linked together. In fact, it has frequently been stated that renal infarction is not followed by an elevation of blood pressure.

The often quoted case of Boyd and Lewis[4] in which relief from hypertension resulted after the removal of a partially infarcted kidney possibly belongs in this group, but cannot be seriously considered because of the lack of specific pathologic details and the suggestion by the authors that widespread vascular changes throughout the kidney had greater significance than the infarct.

Four cases of hypertension due to renal embolism have been reported by Fishberg.[9] In the 1st of these a transient rise in blood pressure of 4 days duration occurred following events which led to a clinical diagnosis of infarction of the left kidney. The 3 other individuals, each suffering from mitral stenosis, developed hypertension which persisted until death, at variable periods after the occurrence of renal artery embolism. On postmortem examination complete occlusion of the main trunk of the right renal artery with massive but not complete infarction of the kidney was observed in 2 instances. No excretion of dye took place on the affected side following intravenous pyelography nor was any urine obtained by ureteral catheter in 1 of these cases. In the 3rd case, the only one in which renal failure developed, the left main trunk and the right middle branch of the renal arteries were involved.

Prinzmetal, Hiatt and Tragerman[23] made a careful study of a patient with chronic rheumatic heart disease who developed hypertension several days after an attack of abdominal pain. Death occurred in uremia 3 weeks later, during which time the elevation of blood pressure persisted while there was progressive suppression of urine and retention of nitrogen. An autopsy revealed thrombotic occlusion of both main renal arteries, probably embolic in origin, and extensive though incomplete bilateral infarction of the kidneys. Perfusates of 1 kidney contained a pressor substance similar to that found in perfusates of ischemic kidneys of animals. In this case the hypertension was presumed to be due to the same mechanism as that responsible for the hypertension following the termination of complete renal ischemia in experimental animals.

From the clinical standpoint, thrombosis of the renal artery has not been stressed until recently. Wolffe,[32] in a report confined almost exclusively to immediate clinical manifestations, discussed 27 cases in which a diagnosis of thrombosis of the main renal artery or its branches was made. The criteria on which the diagnosis was based are not too firmly established since in only 1 instance was postmortem confirmation obtained. However, it is interesting to note that a sudden elevation of blood pressure occurred in a high percentage of the more severe cases.

Saphir and Ballinger[27] were the first to present a detailed report of hypertension associated with thrombosis of 1 main renal artery (Case 1). It concerned a 46 year old male in whom arterial hypertension was first noted 3 years after a fracture of the pelvis. Two years later following an automobile accident, a retroperitoneal mass was discovered in the left upper quadrant. Death occurred in uremia about 9 months later following the development of congestive heart failure, and while the patient was under observation in hospital the blood pressure readings varied from 205/100 to 254/120. Pyelography showed excretory function to be excellent, and the left kidney was depressed by an extrinsic mass. At autopsy the left renal artery was smaller than the right, the orifice was markedly stenosed, and the lumen was almost completely occluded by old organized, partially calcified, thrombus material and some more recent thrombus. The left kidney revealed no abnormality other than a small area of infarction, whereas the right kidney with a widely patent artery presented a typical picture of malignant nephrosclerosis. The mass palpated clinically proved to be an organized hematoma of the left adrenal gland. There can be little doubt that a causal relationship existed between the constriction of the left renal artery and the hypertension. However, the exact sequence of events and the rôle of the thrombosis, exclusive of the other stenosing factors in producing the ischemia, would seem to be matters for speculation.

Two additional cases of unilateral renal artery thrombosis with hypertension, observed by the Reviewer within a period of 5 months, and at present being prepared for publication, will be briefly summarized:

The first patient, a healthy 59 year old male, with no previous complaints referable to his terminal illness, was found to have a systolic blood pressure of between 180 and 190 mm. of mercury 5 weeks after the last of a series of routine periodic examinations. Previous blood pressure readings taken on numerous occasions had averaged 140/80. Hypertension persisted, despite intermittent red rest, over a period of 3 months after which time the patient entered hospital for investigation. Physical examination was essentially negative except for a chronic pansinusitis and a blood pressure of 192/122. A careful study of the genito-urinary tract revealed a small non-functioning right kidney, and a large left kidney with normal function. There was no retention of nitrogen, but the urea clearance was diminished to about 50% of normal. The blood pressure remained at high levels which ranged between 180 to 220 systolic and 120 to 140 diastolic with occasional peaks as high as 250/150 mm. of mercury. Approximately 5 months after the hypertension had been discovered, a right nephrectomy was performed. At operation, which had been delayed for several weeks on account of a troublesome sore throat, no pulsations could be felt in the right renal artery. Postoperatively the blood pressure fell within a few hours to 140/60 and on the following day became stabilized at about 90/60. The patient developed pneumonia and died 40 hours after the operation.

The right kidney, removed surgically, weighed 134 gm. and showed no infarction or other gross abnormalities. Microscopically there was a conspicuous absence of vascular sclerosis affecting either arterioles or arteries. At autopsy the right renal artery, which had been ligated close to the kidney, was occluded near the aorta by a mass of thrombus material 6 mm. in length. The central part of this thrombus was organized and recanalized while at either end it appeared more recent and was undergoing organization. The abdominal aorta was the seat of marked arteriosclerosis but in both renal arteries atheromatous changes were minimal. The left kidney weighed 255 gm. and the histologic appearance was that of extreme hypertrophy. In this, the unobstructed kidney and in other organs, notably pancreas, adrenals and liver, there was a diffuse hyaline thickening of small arterioles. The heart was hypertrophied and there was a widespread, early, acute bronchopneumonia in both lungs.

It is impossible to determine whether the arterial occlusion resulted from thrombosis *in situ* or embolism from a mural thrombus in the abdominal aorta, but since the age of the thrombus in the right renal artery could readily approximate the 5 months duration of the hypertension, it seems reasonable to assume that occlusion of this vessel with the resulting unilateral ischemia initiated the sudden elevation in blood pressure.

The second case is that of a 55 year old male who was admitted to hospital with a diagnosis of hemorrhage from a gastric ulcer. There was no previous history of hypertension, but despite a considerable degree of exsanguination over a period of 2½ weeks the blood pressure readings averaged 150/90. During this time transfusions and conservative treatment failed to cause improvement and the hemorrhage was finally arrested by a widespread ligation of blood-vessels supplying the lesser curvature of the stomach. Shortly after this operation the blood pressure rose to 200/100 and remained at consistently high levels up to 260/150. The patient had a convulsive seizure on the second postoperative day. Following this, during a period of improvement, an intravenous pyelogram failed to show any excretion of dye on the left side and retrograde studies revealed a small left kidney without appreciable function but with a normal pelvis and ureter. Renal function was fairly good as indicated by a 40% excretion of phenol sulphonphthalein in 2 hours and a blood non-protein nitrogen level of 32.8 mg. per 100 cc. These studies suggested that an anomalous left kidney might be the cause of the hypertension and left nephrectomy was planned. However, before this could be carried out, the patient had a second generalized convulsion followed by death 2 weeks later and 6 weeks after the gastric operation.

At autopsy the main branch of the left renal artery was completely occluded near its orifice, by a relatively recent, organizing thrombus. This blocked the lumen for a distance of approximately 1 cm., had occurred over an area of moderate arteriosclerosis and appeared to have been present for at least 4 to 6 weeks. The lower abdominal portion of the aorta showed marked arteriosclerosis. The left kidney was atrophic, weighing only 75 gm. and contained a recent infarct at the upper pole posteriorly, related to a small, somewhat narrowed, extrarenal branch of the renal artery. Microscopically, the non-infarcted tissue appeared slightly condensed but otherwise normal, and there was no suggestion of arteriolar sclerosis. The right kidney was relatively hypertrophied, weighing 180 gm. and on histologic examination, numerous thickened, hyaline arterioles were encountered. The heart was not appreciably hypertrophied.

There is little reason to doubt that the hypertension, at least at its

terminal level, was related to the profound circulatory disturbances in the left kidney. The postmortem findings do not suggest that either the hypertension or the renal artery thrombosis had been present before the terminal illness, and it is quite possible that a sudden onset of hypertension shortly before admission to hospital precipitated the gastric hemorrhage. On the other hand, the occurrence of thrombosis or embolism at the time of operation cannot be entirely excluded.

Congenital Lesion. The well known and frequently quoted case of Leadbetter and Burkland[15] still remains the most clear-cut and possibly the only convincing human counterpart of the "Goldblatt phenomenon" as seen in experimental animals. In this instance a colored boy was found to have an enlarged heart at the age of 6 months. Hypertension was definitely established when the child was 3 years old and the first blood pressure determinations were made. Further studies at this time disclosed an ectopic right kidney. No relationship between the hypertension and the ectopic kidney was considered until 2 years later when nephrectomy was performed. The lumen of the right renal artery was found to be almost completely occluded by a mass of smooth muscle, a lesion which was probably congenital in origin. The blood pressure fell promptly after operation to a relatively normal level and a subsequent report published 3½ years later stated that there had been no return of the hypertension.[6] At this time the child, aged 9 years, was healthy and active with a blood pressure stabilized at about 105/65 mm. Hg.

Narrowing Due to Extrinsic Factors. Kinking and Torsion. Obstruction of the renal artery due to rotation and twisting of the pedicle of a movable kidney should theoretically correspond in some measure to intermittent clamping of the renal artery in experimental animals; but orthostatic hypertension is apparently not very frequently associated with nephroptosis. However, McCann and Romansky[20] demonstrated quite clearly, in a small group of cases with nephroptosis, that the blood pressure was elevated and that the total renal blood flow was diminished in the erect posture as compared with the findings when the individuals were recumbent. Their postulation of a transient interference with the blood supply of the kidney resulting in increased renin production, under these conditions, seems quite reasonable, although attempted fixation of the kidney by nephropexy or the application of a belt did not appreciably reduce the blood pressure.

Riskind and Greene[26] subsequently reported the case of a 47 year old woman, suffering from menopausal symptoms, whose blood pressure over a 2 year period ranged between 170/100 and 220/120. Complete bed rest in the horizontal position lowered the blood pressure to some extent and retrograde pyelography revealed no abnormalities in the recumbent position. However, in the upright position a 45 to 60 degree torsion of the pelvis on the right side was noted. The patient's course was reported for 1 year after the application of a corset, during which time a relatively normal blood pressure was maintained except for occasional periods when high levels were recorded. These were usually associated with removal of the corset.

The relatively scant data in this field suggest a definite relationship between the hypertension and disturbances in renal blood supply, but the rôle played by such factors as obstruction to the venous return from the kidneys and to the outflow of urine needs further elucidation.

Aneurysm of Renal Artery. Aneurysms of the renal artery; although questionably producing occlusive lesions, will be briefly discussed. Howard,

Forbes and Lipscomb[13] were perhaps the first to draw attention to the possible relationship between this relatively uncommon condition and hypertension. They reported the case of a 5 year old girl whose blood pressure was known to be within normal limits 6 months before the occurrence of a small cerebral hemorrhage in the right frontal region. The blood pressure at this time ranged between 158/90 and 200/140. Hypertension persisted and retrograde pyelography on 2 occasions revealed no abnormality. The urine contained a few casts and a trace of albumin. A right lumbar sympathectomy had no effect on the blood pressure and 2 weeks later during a sympathectomy on the left side, a thin-walled, multilocular, pulsating mass was found attached to the left renal artery. The vessel was ligated through the mass and the left kidney was removed. The blood pressure which was 170/100 before nephrectomy fell within 5 minutes to 140/90 and remained at slightly elevated levels in the neighborhood of 125/90 for 9½ months. Interpretation of this case is extremely complicated, since a possible effect of the bilateral sympathectomy cannot be excluded, and pathologic examination of the kidney removed at operation revealed subchronic glomerulonephritis. This was presumably related to an attack of acute hemorrhagic nephritis diagnosed when the child was 2 years of age and could readily account for the postoperative persistence of a slight elevation of blood pressure and moderately lowered urea clearance.

All previously reported cases of aneurysm of the renal artery were reviewed in 1932 by Mathé[19] and the review was brought up to date in 1943 by Lowsley and Cannon.[18] In only 4 of the first group of 56 cases was hypertension noted while 2 others showed cardiac hypertrophy. In the later series, hypertension was present in 4 out of 21 cases and was apparently cured by nephrectomy in 1 instance. It is, of course, quite possible that an aneurysm in this location could alter pulsation within the kidney or cause ischemia by direct pressure on the renal pedicle, but available data provide little more than a suggestion of an occasional association between this type of lesion and hypertension.

External Pressure. Reported cases of hypertension associated with constriction of one or both renal arteries by pressure from without are few in number and the actual frequency of such an association is probably not accurately reflected in the literature. The 4 cases reviewed below illustrate the pressure effects of widely different lesions. They are pertinent to the present discussion, because each is cited by the respective authors as an example of the operation, in man, of the Goldblatt mechanism of the production of hypertension.

In the case of Blatt and Page[3] a male aged 38 years died about 11 months after the onset of symptoms referable to a widespread lymphosarcoma. Early in the course of the disease he developed a persistent hypertension and at autopsy a large mass of tumor tissue was found enveloping the kidneys, renal vessels, ureters, abdominal aorta, inferior vena cava and adrenal glands. Some evidence of early glomerulonephritis was also found on histologic examination of the kidneys. Although fully aware of the numerous possible factors in this case that might have been responsible for the development of hypertension, the authors stress partial constriction of the renal arteries as the most important single factor.

The association of a large hydatid cyst of one kidney with a clinical picture of malignant hypertension and the typical changes of malignant nephrosclerosis in the opposite kidney was reported by Davson.[7] Although partial occlusion of moderately large branches of the renal artery was demonstrated at autopsy, the simultaneous occurrence of dilatation of the

renal pelvis with compression and fibrosis of kidney parenchyma makes an exact reconstruction of the mechanism of disturbed blood supply impossible in this instance.

A more clear-cut example of hypertension related to external pressure on one renal artery is found in the case described by Hoffman.[12] This concerned a 28 year old negro with syphilis and hypertensive heart disease. Death occurred about 1 year after the onset of symptoms, and a postmortem examination revealed a saccular aneurysm of the aorta, 6 cm. in diameter, which was wedged between the aorta and the left kidney, causing marked compression of the renal artery and vein. The kidney with the disturbed blood supply was atrophic, whereas the opposite kidney was hypertrophied.

In contrast to the 3 previous fatal cases, the last to be described, reported by Farrell and Young,[8] was apparently cured by nephrectomy. An 18 year old male was found on routine examination to have a blood pressure of 154/102 mm. of Hg and physical examination revealed a large mass in the region of the right kidney. An intravenous pyelogram showed no abnormality but on retrograde pyelography distortion and displacement of the right renal pelvis was noted. The right kidney, removed at operation, was encased in a large cystic structure, diagnosed pathologically as an old organized and partially calcified hematoma, which probably resulted from an injury incurred when the patient was 6 years of age. Two thickened and narrowed renal arteries entered the kidney through the wall of the cyst which presumably also surrounded the renal veins. Histologic changes in the kidney were minimal. The mechanism of production of the hypertension in this case was thought to be similar to that in experimental cellophane perinephritis, but it is difficult to exclude the effects of compression of the extrarenal blood-vessels.

In all instances of extrinsic pressure on the pedicle of the kidney, whether associated with hypertension or not, venous or ureteral compression is a distinct possibility, if not an actuality, so that the specific effect of arterial occlusion cannot be clearly evaluated.

Summary and Conclusions. The actual number of reported cases in which hypertension is associated with obstructive lesions of one or both main renal arteries in man is not large and in only a small percentage of these can a definite etiologic relationship be established between the vascular lesion and the elevation of blood pressure. Most of the material reviewed consists of fatal cases in which attempts have been made to correlate postmortem findings with hypertension observed before death. A great deal of indirect, but highly suggestive evidence, in favor of an etiologic association between occlusive lesions of the main renal arteries and hypertension, is supplied by this group of cases, although in many instances exact interpretations are rendered difficult or impossible by the coëxistence of other intrarenal or extrarenal lesions, possibly responsible for the initiation or accentuation of hypertension. In the face of such complicating factors there has perhaps been too great a tendency to assume the action of the "Goldblatt mechanism" merely because of the presence of a lesion which narrowed the lumen of one or both main renal arteries. On the other hand, it is noteworthy that no evidence, opposed to the view that experimentally produced hypertension has a human counterpart, was encountered. From the findings in occasional specific instances, benefited by nephrectomy, it can be reasonably concluded that a mechanism, similar to that responsible for the production of hypertension following the application of a clamp to the main renal artery in

experimental animals, is capable of acting in the human subject. Despite the relatively few reported cases in which occlusion of the main renal artery apparently played a rôle in the production of hypertension, the wide variety of lesions capable of causing arterial obstruction suggests that the action of this mechanism may occur more frequently than is indicated by the literature.

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PREVENTIVE MEDICINE AND EPIDEMIOLOGY

UNDER THE CHARGE OF

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TROPICAL DISEASE AND GLOBAL WAR

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Disease in War Time. Prior to December 7, 1941, few Americans were concerned with the possibility of the entrance of exotic diseases into the continental United States. Public health[35] and military officials,[30] however, have been deeply concerned for many years, fearful of the extension of the plagues of war to this continent. Although war is often limited by political boundaries, disease recognizes no such limitations. Bacteria do not recognize any law and are equally dangerous to friend and foe.

Since the beginning of history, wars[41] have inevitably been attended by pestilence and disease. Throughout the records of man,[28] famine and

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disease are constant companions of war. Their goal is death and destruction. The outcome of campaigns and the course of history have, upon occasion, been determined not by military operations but rather by disease outbreaks and epidemics. Nations have been defeated by war-brought pestilence. Armies[40] have been decimated by malaria, smallpox and plague. European history is, in fact, full of accounts of "French" disease, "Spanish" disease and others where armies have been traveling reservoirs of infection, spreading both endemic and epidemic disease throughout the area which they invaded. The resulting outbreaks have, however, in the main been restricted to zones of military operations and only rarely followed the soldier on his return home from distant war fields.

Prior to the 20th century,[6] wars were characterized by great epidemics of typhus fever, smallpox, typhoid fever, dysentery, malaria, cholera and bubonic plague. In 20th century warfare, influenza, meningococcus meningitis and other respiratory and arthropodal-borne diseases are the chief concern of the military and civilian health authorities. Under war conditions,[13] many of the safeguards of the health of both military and civilian populations are abandoned. The intimate contact between individuals who are herded into concentration or military camps, or who are crowded into bombshelters, or into confined quarters in an effort to keep warm, provides ample opportunity for the transfer of exoparasites or direct infection. Under such primitive environmental sanitation and inadequate personal hygiene, conditions for the spread of infections are ideal. This concentration and movement of armies and refugees, accompanied by the hardships of exposure and fatigue, malnutrition and the lack of proper medical care, provide the fuse for explosion of widespread epidemics.

More soldiers were killed by infectious disease than by bullets in all wars prior to the Franco-Prussian War of 1870, at which time the German armies reported more deaths from battle than from disease. In the Russo-Japanese War of 1904, both sides experienced more disability from war casualties than from infectious disease. Our own A.E.F. of 1917 and 1918,[8] in spite of the toll of influenza, reported fewer deaths from sickness than from battle. If, however, the data for the entire United States Army, at home and abroad, are taken into account, the deaths from disease in those years were more numerous than those from battle casualties.

World War I. During and after World War I, all infectious diseases normally prevalent, except the common childhood diseases, were highly prevalent in eastern Europe. There was an epidemic of typhus fever and relapsing fever through eastern Europe, especially Russia, Poland and Siberia. Fortunately, these diseases did not spread into western Europe and to regions where the American army was fighting. Overshadowing all other epidemics was the influenza pandemic which caused an increased fatality from pneumonia. Meningococcus meningitis was epidemic, while dysentery, smallpox, tuberculosis and venereal disease increased in prevalence. Since the vast portion of the fighting in World War I occurred in continental Europe, tropical disease played a relatively minor rôle except for malaria, which became highly epidemic in certain regions of southern Europe. Malaria[18] was victor in Macedonia and decimated the opposing armies to a pathetic ineffectual fraction. Although it had previously disappeared from most of Europe,[5] malaria returned with the soldiers and refugees to central and northern Europe to ravage the civilian population for over a decade. The United States, fortunately, escaped the importation of tropical diseases which were stirred up in that conflict. Since our armies did not fight in the areas where these diseases were prevalent, they did not succumb to them; nor did they bring them back upon their return.

THE PRESENT WAR. This global war[31] is much more hazardous to civilian populations than any in history. Zones of intensive military activity extend to all continents, into jungles, subtropical and tropical countries and areas where tropical diseases are endemic, if not hyperendemic. The civilian population in these regions is being exposed to additional hazards caused by the shifting of military populations, and civilian populations behind areas of military operations are exposed to the potential hazards of disease returning with the moving troops. The mass movement of refugees and of routed armies particularly predisposes to the spread of infectious disease. It is probable that the peak of infection will not reach its maximum until after the cessation of actual warfare, and it is probable that with the ensuing transfer and readjustment of population, a return to the usual prevalence of infectious diseases may not be expected for many years.

With battles raging in all parts of the globe, especially the tropics and subtropics, the military personnel is exposed not only to the classical war diseases but to many new hazards. Most important of these are the infectious tropical diseases[29] which for generations have subjugated native races.

Large numbers of non-immune, susceptible individuals are being concentrated into areas where so-called tropical diseases are prevalent. Although under peacetime conditions,[33] known effective control measures can reduce the rates of many of these diseases to a minimum, under battle conditions it is often impossible to apply preventive measures. The personnel is, therefore, afforded only limited application of control measures and is often exposed to infection of tropical diseases under most trying circumstances. An entire new galaxy of tropical diseases faces the soldier as he struggles through tropical jungles and swamps, through native settlements whose populations are overflowing caldrons of infection.

Prevalence of Tropical Diseases. For many years, tropical diseases[47] were regarded as indigenous only in tropic and subtropical areas; but today it is known that the term "tropical"[10] must be interpreted rather as the usual abode of these diseases, but by no means their geographic limitations. Yellow fever, for example, has been epidemic at times in most of the ports along the Atlantic Seaboard as far north as Boston and New Bedford. Fortunately, these outbreaks were limited to the summer and died out with the onset of cold weather.

Filariasis was formerly endemic in South Carolina. Dengue[3] has been endemic along the Gulf of Mexico Coast for generations. Murine typhus[11] has been endemic along the Pacific, Atlantic and Gulf of Mexico Coasts. Cholera has been epidemic in most of America's seaports. Relapsing fever has been reported from the Pacific and western states. Kala-azar (*Leishmania donovani*) has been reported from the southwestern states. Malaria has existed in the United States since the earliest colonial times, and about 1,000,000 new cases are reported annually. In 1935 the death rate from malaria for the United States[43] was 3.5 per 100,000; in 1941 it reached the low rate of only 0.9.

Tropical diseases[29] are more prevalent in the warmer regions, and are due to all types of etiologic agents, bacterium, virus, rickettsia, protozoa or metazoa parasites. Many require particular intermediate hosts and special arthropodal vectors. Some of these diseases are limited by special factors such as climate, distribution of the intermediate hosts, availability of the arthropodal vector[22] or carrier and so forth. A few of these arthropod-borne tropical diseases are a menace to the United States, as malaria.

Other tropical diseases, which are spread by the lack of proper sanitation and personal hygiene, tend to have world-wide distribution in areas of poor sanitation; but these should be of no serious danger to the civilian population of the United States unless there is a breakdown in water and sewage disposal facilities.

Two important problems face civilian physicians and health officers in the United States: (1) the diagnosis and treatment of the returning personnel who may be infected with a tropical disease; (2) the possible importation[27] of tropical disease into the United States.

Diagnosis and Treatment. Probably no branch of medicine has advanced as rapidly in diagnosis and treatment as has tropical medicine in the past 50 years. Schools and institutes for research in tropical medicine are increasing in number and in geographic spread, until now almost every country has one or more centers for the study and teaching of tropical medicine.

The Army and Navy medical authorities[26] have felt that the subject of tropical medicine has not been taught with sufficient thoroughness in the medical schools of this country. Consequently, these services have made provisions for supplementary training of their medical personnel in the treatment and control of these diseases. Moreover, a plan for the improvement of the teaching of tropical medicine in the medical schools of the United States and Canada has been developed through the coöperation of the Association of American Medical Colleges, the John and Mary R. Markle Foundation, the Office of the Surgeon-General of the U. S. Army, the National Research Council, the Army Medical School and Tulane University. The plan consists in offering to each medical school an opportunity for 2 members of its staff to attend a course in tropical medicine. Medical schools, in turn, have expanded their teaching of tropical medicine, and many physicians are now treating these diseases, as military activities enter areas of tropical disease prevalence. However, not all cases of tropical diseases will be diagnosed, treated or cured by military physicians. Some patients may not develop symptoms until after discharge and return to their homes, whereas others may have recurrences or unrecognized infections; many of these will come to the family physician for treatment.

Not all diseases[4] contracted in the tropics are necessarily exotic diseases. The attending physician must bear in mind the fact that diseases of the temperate climate also exist in the tropics[46] and that these must be considered in the differential diagnosis of an illness in a patient who has returned from the tropics.

As Strong[47] ably indicates—one of the first questions to be asked a man suspected of having a tropical disease is, "Where have you been during the past months and years?" Thus, from a knowledge of the geographic distribution of diseases, the physician can obtain a clue. The diagnosis of tropical disease, as with other infectious disease, depends upon the patient's history, the physical and laboratory examination, and the physician's knowledge of the disease involved. It has been emphasized that tropical diseases do not necessarily predominate in most tropical countries. Moreover, these diseases may present an unusual or bizarre picture in temperate zones. If the attending physician, after a careful history and examination, suspects the existence of a tropical disease, it is best to call a consultant who is experienced in the diagnosis and treatment of these diseases.

Importation Into United States. The health of the individual is no longer his sole responsibility and affair. The community is concerned

especially with any case of infectious disease which may act as a focus of spread. Certainly, a case of active malaria is of concern to a health officer in a New England community where *Anopheles quadrimaculatus* abound. Similarly, dengue is important to the southern community, and such diseases as bacillary dysentery, cholera, plague or typhus are of concern to every health officer. Recognizing the potential dangers[7] of the importation of tropical diseases, the Army[38] and Navy,[36] in coöperation with the United States Public Health Service, are preparing detailed plans to protect the civilian population against extensive exposure to these diseases. Moreover, these services[25] have taken every known control measure against tropical diseases. Through active research, in coöperation with various civilian groups, they have developed additional protective measures.

Control by the Army and Navy. Personnel of the military services[9] receive routine vaccination against smallpox, typhoid and paratyphoid A and B. All military personnel on induction are now immunized, as in the Army,[24] by 3 injections of plain or liquid toxoid or, as in the Navy and Marine Corps,[26] by 2 injections of alum-precipitated tetanus toxoid.

Yellow fever vaccine, manufactured by the United States Public Health Service and the Rockefeller Foundation, is administered to all personnel about to depart for areas in which the disease is prevalent. Under similar circumstances, typhus, cholera and plague vaccines are used. Although the yellow fever vaccine is of proved value, the plague and cholera and typhus vaccines are yet in the experimental stage, but are believed to be of value in the reduction of both mortality and morbidity. General Simmons[42] regards the present immunization program as one of the most potent weapons being used for the preservation of the health of the Army.

The Army[42] established a Preventive Disease Division of the Surgeon-General's office in 1941. The objectives of the division have been the maintenance and conservation of the health of the Army through the prevention and control of infectious diseases and the elimination of sanitary, occupational and other health hazards.

This division includes branches of Sanitation, Sanitary Engineering, Epidemiology, Laboratories, Military Occupational Hygiene, Venereal Disease Control and Medical Intelligence. The Sanitation branch is concerned with the eradication of biting insects, the protection of troops against mites, ticks, lice, bed-bugs, fleas, mosquitoes, sandflies, gnats and biting flies, and with sanitation of water, food and wastes. The Sanitary Engineering branch is concerned with sanitary control of large water purification plants and sewage disposal plants of a permanent nature. With the Corps of Engineers, it initiates and plans insect and rodent control programs for posts in the zone of the interior. In the branch of Epidemiology, the section on tropical diseases initiates programs for the control of these diseases. These programs include the organization of special teams of highly trained control officers, extensive training of medical personnel and the development of new procedures for the control of tropical infections among troops.

A civilian commission on tropical diseases, headed by Dr. Wilbur A. Sawyer, assists and advises the Army in its fight against these diseases. The Medical Intelligence branch collects, assembles and disseminates to troops embarked for a particular area all medical information which may be of value in protecting the troops. For example, if malaria is prevalent in that region, then information as to the anophelines, the breeding and

feeding habits, is included. After collection, the data are studied and used to prepare comprehensive health surveys containing data on topography, climate and population of the country, a section on the public health services and facilities for sanitation and medical care, and detailed information concerning the important diseases and their epidemiology. These surveys are distributed to commanding officers and medical officers of all forces going to foreign countries. They are used as a basis for the specific recommendations made for the protection of all troops sent abroad.

The Navy[23] provides medical officers with special training in tropical medicine, and has recently revised a bulletin "Notes on Tropical and Exotic Diseases of Naval Importance."[24] The purpose of these notes is to present useful and up-to-date information on certain tropical and exotic diseases with which naval medical officers may have had limited experience. The bulletin contains an abundance of maps in color, depicting the geographic distribution of tropical diseases. To Navy personnel 4 groups of disease are of greatest danger: malaria, dengue, dengue-like fevers (sandfly fevers) and dysenteries (bacillary and amebic). Diseases listed as potential hazards, which do not occur or rarely occur at present among Navy personnel are: typhus and rickettsial diseases, cholera, yellow fever, plague, filariasis, the relapsing fevers, infectious jaundice and other leptospiroses and Bartonelloses (Oroya fever—*Verruga peruana*). Other diseases, such as hookworm infestations, schistosomiasis, trypanosomiasis, leishmaniasis, leprosy, yaws and pinta, are described as of secondary or little importance and are not apt to be of widespread occurrence or to cause great disability among Navy personnel.

Although the possibility of the importation of tropical disease into the United States and in fact to all parts of the world, such as Australia and Great Britain, where these diseases are not usually prevalent, has been overemphasized, nevertheless this hazard does exist. In spite of all the precautions taken by the Army,[19] Navy[20] and the Public Health Service, not all cases will be identified, and not all returning ships and planes will be entirely without danger of transporting insects or rodents which may act as foci.

Methods of Importation. A tropical disease may gain entrance into areas where it has not been prevalent by one of several methods:

1. *Disease may be introduced by carriers or cases of which some may not be recognized.* The chances of this type of entrance are greater than ever because of the development of radar and the relative safety of both military and civilian aviation. It is entirely possible for a traveler to leave India and arrive at a Boston airport perfectly well, but later develop bubonic plague which he contracted in India. The problem presented by latent, unrecognized infection and the carrier state among the military personnel cannot be fully appreciated. The danger of importation of disease does not arise from the recognized and treated cases, but from these latent infections and carriers.

2. *Animal reservoirs may be introduced from areas where the disease was indigenous and thereby bring the disease with them.* This is thought to have been the means whereby equine encephalomyelitis[12] was introduced into New England in 1938. Bubonic plague probably entered California by means of infected rats, and now has spread as sylvatic plague to many wild rodents in the Pacific and western states as far east as the Mississippi.

3. *Insect vectors may be brought by aeroplanes, ships, or other means of transportation.* Yellow fever was brought into Boston by clipper ship; *Aëdes ægypti* mosquitoes bred on shipboard in open casks of fresh water.

The recent outbreak of malaria in Brazil[45] was due to the importation of *Anopheles gambia* from Africa by aeroplane.

Jackson[21] lists cholera, plague, smallpox, typhus, yellow fever, malaria and dengue as diseases of 2 day to 2 week incubation periods, and that they may. appear among the passengers of an air transport after their arrival in this country from a port where these diseases are prevalent. Insects, he states, may be carried not only in the interior, but also in depressions of the exterior of the plane. Recently, special disinsectization procedures have been applied to the retractable landing gear of planes, as it was discovered that on retraction within the fuselage an excellent means of hiding was provided for a variety of insects. Recently *Anopheles albimanus* was captured near a Florida airport. As this mosquito is not a native of North America, its means of ingress seems obvious. Several procedures, depending upon the type of disease concerned, are applicable to the control of air-borne transfer of disease: (*a*) vaccination of personnel and of passengers if indicated; (*b*) inspection of passengers prior and subsequent to flight; (*c*) issuance of travel certificates, listing the date and place of departure; (*d*) spraying of the interior of planes ½ hour prior to landing and complete internal and external disinsectization upon arrival; (*e*) inspection of baggage; (*f*) delousing of clothing and personnel from typhus infested ports.

4. *The disease may find new hosts in the new area.* Examples of diseases which can adapt themselves to a variety of animal hosts are plague, tularemia and brucellosis. Equine encephalomyelitis[12] has been demonstrated in a vast variety of animals, such as horses, mules, domestic fowl, pigeons, ringed neck pheasants and a variety of other wild birds.

5. *The disease may find a new insect vector in the area invaded.* The transmission of yellow fever in different areas is an illustration of the adaptability of various insects to the spread of this disease. Nine species of *Aëdes* mosquitoes and some of the members of the genera *Eretmopodites*, *Culex*, *Mansonia* and *Anopheles* have been shown to transmit the virus of yellow fever in West Africa.

6. *New or different strains of the disease may be introduced into an area where less virulent strains were formerly prevalent.* This is illustrated by the introduction of malignant malaria (*Plasmodium falciparum*) into areas where benign malaria (*Plasmodium vivax*) was formerly prevalent. As little or no cross-immunity exists between these 2 types of malaria, the more virulent type will cause a widespread outbreak with many resultant deaths. Similarly, there is the possibility of the importation of the Shiga variety of bacillary dysentery into the United States.

Naturally, here in the United States, health authorities are not so much concerned with the possibilities of tropical disease among the civilian populations of Europe, Asia and Africa as in the possibility of their importation into the States. On this point, one can feel rather reassured; it is extremely unlikely that any tropical diseases, not already prevalent, will become indigenous in this country. In fact, the northern states are relatively safe from most of the tropical infections, and even if latent infections and carriers return to local communities there will be only rare cases, if any, of these exotic infections. The problem in the southern states is, however, more serious.

Some of these so-called tropical diseases are endemic now in this country[34] and, although additional carriers[14] may bring their infections into local communities, few additional cases will result as long as proper sanitation and personal hygiene are maintained. This fact is especially applicable to

the enteric diseases,[2] such as typhoid, paratyphoid, bacillary and amebic dysentery. So long as excreta are properly disposed of, and so long as carriers of these organisms wash their hands thoroughly after going to the toilet and before handling food, there is no danger of an outbreak.

Bacillary dysentery[37] is perhaps one of the most important military diseases of the war. Fortunately, treatment with sulfaguanidine not only shortens the clinical course of the disease, but reduces the length of the carrier stage which usually follows. Nevertheless, asymptomatic carriers[1] and latent infections will occur among returning troops,[49] and there may be an increase in the types of Shigella already prevalent; and in addition other types may be introduced. Similarly, Salmonella outbreaks may result. Great care must be exercised in preventing[16] outbreaks due to food handlers who are carriers of Shigella or Salmonella organisms.

Typhus fever, relapsing fever and other louse-borne[15] diseases are another group of tropical infections which are not likely to find a foothold in most of the country. There was a time when some of the immigrants did not regard themselves as virile unless they were lousy—infected with lice. At present, however, body lice are a rare finding in New England, but are still not uncommon among negro and other racial groups, especially in the South and southwestern states. With adequate use of hot water and soap—the American traditional Saturday night bath—the public can remain free of lice and thereby prevent the spread of louse-borne diseases. If the rat population were immensely increased by enemy destruction of cities, and if municipal sanitation standards were broken down, then there might be danger of an outbreak if lice and the infecting organisms were introduced. Under a similar breakdown of sanitation, outbreaks of cholera would be possible. However, since there are good reasons to believe that enemy massive destruction is unlikely, and since the possibility of introducing these infective agents is remote, there need not be concern about such diseases as typhus fever, relapsing fever, bubonic plague and cholera.

Dengue and yellow fever[39] are 2 other diseases which are unlikely to be prevalent, except in the southern states, as the mosquito vector is limited almost entirely to the area south of the Mason and Dixon line, and the infecting organism must be imported. The *Aëdes ægypti* mosquito, the vector of these infections, cannot survive northern winters; under most unusual conditions, therefore, it is possible, although highly improbable, that these 2 diseases may gain temporary access even in northern communities. Such outbreaks would naturally disappear spontaneously with the onset of cold weather, and would not reappear again unless reintroduced. Dengue, of course, is endemic in the South, and it is possible that the disease may temporarily become more widespread. However, the United States Public Health Service[35] has undertaken control programs in Texas, Alabama and Florida against *A. ægypti*, and this fact, together with the factors already limiting this disease, would continue to prevent its extension for any great length of time.

Perhaps the disease which may cause most civilian concern in the United States is malaria. Malaria has been endemic throughout most of the United States as far north as Canada. In New England there have been at least 3 epidemic waves, 2 of which spread up the rivers from Long Island Sound to Connecticut and Massachusetts. During the first decade of the 20th century, the disease was still endemic in some parts of New England, but for almost 20 years only rare cases have been reported. In Massachusetts,[17] during the past 14 years, there have been only 11 reported

cases of malaria in persons who were never out of that state and who apparently acquired the disease within the state as a result of mosquito bites. Fortunately, climatic conditions and land improvements have been unfavorable to the continued existence of malaria in New England and the northern states. In the South, intensified malaria-mosquito control programs have been, in the main, responsible for the reduction in malaria infections. With the building of each house and the cultivation of each new farm, additional mosquito-breeding places are destroyed.

At present, health authorities are convinced that the concentration of *Anopheles quadrimaculatus* in the northern states is not sufficient to maintain malaria at an epidemic level. However, if carriers of malaria return, they may act as foci of small local family or neighborhood outbreaks. Adequate treatment of all cases and proper screening of houses are, however, excellent control measures. Both the Army[43] and Navy are treating all cases, and any soldier or sailor who is discharged with malaria is carefully followed up by the state departments of public health. All measures are taken to protect the public.

In the South[44] the danger from malaria is, of course, much more serious, as the concentration of *A. quadrimaculatus* is far greater, the mosquito season is longer, and screening of houses is not as adequate. The United States Public Health Service has taken cognizance of this fact and through its program, "Malaria Control in War Areas,"[48] has limited all of its mosquito-control work south of the Mason and Dixon line. North from here, the "M. C. W. A." has limited its work to mosquito surveys in the immediate environs of military hospitals and institutions where patients ill with malaria are likely to be hospitalized.

A few cases of plague, cholera, leprosy, yaws, leishmaniasis, trypanosomiasis, schistosomiasis, or other helminth infections may occur among troops coming into close contact with native populations. Phlebotomus fever and filariasis may incapacitate a considerable number for future military service in the tropics, but it is not likely that the latter will become endemic again in this country. These diseases will present problems of diagnosis and treatment, but are not likely to gain endemicity or even temporary epidemicity in the United States. As Meleney[32] well summarizes: "It may be stated with considerable confidence that the chief hazards in the importation of exotic diseases are from the introduction of new strains of parasites already present, and the introduction of new vectors of disease."

Conclusion. Wars have always been accompanied by increases of infectious diseases. In this global war, zones of military operations are extended into areas where tropical diseases are prevalent. American forces face not only the hazards of battle but the classical war diseases augmented by limitation in the application of control measures against the more exotic diseases. Although the Army, Navy and United States Public Health Service are taking all steps to protect our military personnel and prevent extension of tropical diseases to the civilian population, not all cases will be detected before discharge.

The civilian physician is, therefore, faced with the diagnosis and treatment of discharged service men who may have contracted tropical disease. Simultaneously, health authorities are concerned with the possible importation of these diseases. Fortunately, tropical diseases are not likely to bring about any major catastrophe in this country. Because of climatic and environmental factors, tropical diseases do not find favorable conditions for epidemic prevalence. The same factors, which in the past have been gradually bringing about the diminished endemicity of malaria and dengue, will continue to operate and will be aided by extension of control

measures if these are indicated. Malaria is indubitably the most serious problem, and even this disease is not likely to cause extensive outbreaks so long as health authorities are prepared to instigate intensive control measures. Perhaps the only diseases, which will cause any significant increase in incidence, are the enteric infections such as salmonella and shigella. The other tropical diseases are not a menace to the public and, although sporadic cases and even localized outbreaks may occur, not too much concern need be expressed. It is well to remember that military and health authorities are cognizant of the dangers and that all possible steps are being taken to protect the civilian population against the importation of tropical diseases.

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PHYSIOLOGY

PROCEEDINGS OF

THE PHYSIOLOGICAL SOCIETY OF PHILADELPHIA

SESSION OF JANUARY 18, 1944

"Bound" Sulfonamide Compounds in Plasma With Special Reference to Renal Clearance of Various Sulfonamides. J. G. REINHOLD, H. F. FLIPPIN, A. H. DOMM and L. POLLACK (Biochemical Laboratory, Phila-

delphia General Hospital). A variable but often considerable fraction of sulfonamide compounds present in plasma fails to filter under pressure through cellophane membranes. The most important factor determining the proportion so retained, besides the structure of the sulfonamide compound itself, is the concentration of protein in plasma, especially the albumin. Sulfonamide so bound in a protein-sulfonamide complex appears to be in equilibrium with the free sulfonamide and plasma protein. The penetration of sulfonamides into erythrocytes and other cells, and into cerebrospinal and other body fluids, including the glomerular filtrate, is confined to the ultrafiltrable fraction. The renal clearance of sulfathiazole in man, when calculations are based upon its concentration in plasma ultrafiltrate, is equal to the inulin clearance. Thus sulfathiazole is excreted solely by the glomeruli without tubular secretion or reabsorption. Sulfadiazine and sulfapyridine, on the other hand, are reabsorbed to a considerable extent by the tubules.

The ultrafiltrability of serum sulfamerazine has been studied in a group of patients receiving treatment for pneumonia or meningococcic meningitis. Strikingly decreased ability to bind sulfamerazine has been observed in some individuals in the presence of exceptionally severe or fatal illness.

Tests of Pyrogenicity, Antigenicity, and the Efficacy of Ossein Gelatin Preparations* in Repeated Massive Hemorrhage and Infusion. W. M. PARKINS, L. H. SAXE and H. M. VARS (Harrison Department of Surgical Research, Schools of Medicine, University of Pennsylvania). Standard pyrogenicity tests of 8 different lots of 4 and 6% gelatin solutions prepared specifically for infusion purposes were negative.

Ossein gelatin (Lot P 4-20) has been tested serologically in rabbits and for anaphylactic symptoms in rabbits and guinea pigs after sensitizing doses of gelatin and beef serum. This gelatin apparently is non-antigenic and free from sensitizing impurities.

Forty-seven dogs, under light nembutal anesthesia, were bled (4 cc. per kilogram per minute) to a blood pressure end-point of 20 mm. Hg and then immediately infused with a volume of saline, gelatin or pooled heparinized dog plasma equal to the bleeding volume. One hour after initial hemorrhage in some groups, and 3 hours after infusion in others, a 2nd hemorrhage was performed, at the same rate and to the same endpoint as the initial hemorrhage.

The average bleeding volume (cc. per kilogram) of the 2nd hemorrhage expressed as percentage of initial bleeding volume (5 dogs) was as follows: (*a*) 1 hour after initial hemorrhage—saline, 49; 4% gelatin (P 4-20), 100, (P 1-20), 95 and (P 2-20), 100; plasma, 75; 6% gelatin (P 7-20), autoclaved 20 minutes, 117, and (P 7-180), autoclaved 180 minutes, 108. (*b*) 3 hours after 1st infusion—gelatin (P 7-20), 84; (P 7-180), 65; saline, 36; plasma, 65.

The more marked hemodilution (hematocrit) and increase in blood pressure, as well as a higher concentration of plasma gelatin after infusion of 6% gelatin autoclaved 20 minutes, as compared with the 4% and 6% autoclaved 180 minutes, support the following conclusions from bleeding volume determinations: (1) 6% solutions appear more effective than 4% gelatin. (2) Prolonged autoclaving which markedly decreases colloid size, gelatin and viscosity, and increases osmotic pressure, somewhat

* Gelatin preparations were supplied by Dr. D. Tourtellotte of the Chas. B. Knox Gelatine Co., Johnstown, N. Y.

reduces the efficacy, as determined at the 1 and 3 hour intervals. (3) All these gelatin solutions compared favorably with plasma in these hemorrhage experiments where infusion is immediate.

According to the criteria used in experiments now in progress, plasma or whole blood appears to be superior to gelatin when a period of severe hypotension (30 to 35 mm. Hg) is extended to 1 hour before infusion, at which time factors in addition to blood volume, such as peripheral resistance, myocardial and metabolic deficiencies may be involved.

Some Clinical Experience With Gelatin as a Plasma Substitute. C. E. Koop, A. G. Fletcher, Jr., and C. Riegel (Harrison Department of Surgical Research, Schools of Medicine, University of Pennsylvania). One hundred patients have been given 190 intravenous infusions of an especially prepared ossein gelatin totaling 132 liters. The toxicity studies on dogs previously reported to this society have been extended to human subjects. Observations have been made on the effect of single and repeated intravenous gelatin infusions on serum proteins, bromsulphalein retention, urea clearance, blood coagulation and sedimentation rate.

There is a reciprocal relation between the concentration of serum proteins and gelatin protein in the circulating blood after gelatin infusion. The serum protein values are temporarily depressed and rapidly return to normal as the gelatin disappears from the blood stream over a period of 3 to 5 days. Bromsulphalein retention did not occur, and urea clearance tests indicated no renal impairment after infusions of 1000 cc. in 90 minutes. Blood coagulability was not altered, but the sedimentation rate was increased. Histologic examination of autopsy material revealed minor changes similar to those previously reported in dogs.

Clinical studies included observations on blood pressure, pulse, respiration and temperature. No pyrogenic or antigenic reactions were seen. Venous pressure was consistently elevated and cardiac output was increased. Gelatin was used therapeutically in the treatment of acute hemorrhagic shock and edematous states and as a general postoperative measure in surgical cases.

The following conclusions were reached: Intravenous gelatin solutions are easily and safely administered to human subjects. The material is an effective agent in the treatment of at least the early stages of hemorrhagic shock. After major operative procedures the administration of gelatin produces a favorable response similar to that observed with plasma infusions. In certain types of edema there is, following the administration of gelatin, a diuresis which is accompanied by clinical improvement. Further studies on the value of gelatin in shock, burns and hypoproteinemic states are clearly warranted.

BOOK REVIEWS AND NOTICES

THE FOOT. By NORMAN C. LAKE, M.D., M.S., D.Sc. (LOND.), F.R.C.S. (ENG.), Senior Surgeon and Lecturer on Surgery, Charing Cross Hospital; Surgeon, Bolingbroke Hospital; Consulting Surgeon, Emergency Medical Service; Director of Studies, London Foot Hospital; etc. Third Ed. Pp. 432; 136 figs. Baltimore: The Williams & Wilkins Company, 1943. Price, $5.00.

THIS little treatise on the foot is excellent. The author spends much time on the evolution of the foot and reviews the disabilities whether they are due to congenital causes, infections or injuries. He achieves a well-balanced book which can be profitably used by the medical student and general practitioner. He handles the matter of the various operations at times necessary on the foot with well-balanced judgment. This third edition provides an opportunity for the author to include his comments upon foot disabilities from wartime causes.

P. C.

SYMPTOMS AND SIGNS IN CLINICAL MEDICINE. An Introduction to Medical Diagnosis. By E. NOBLE CHAMBERLAIN, M.D., M.Sc., F.R.C.P., Lecturer in Medicine, University of Liverpool; Physician to Out-patients, Royal Liverpool United Hospital, Royal Infirmary Branch; Visiting Physician, Smithdown Road Hospital, Liverpool. Third Ed. Pp. 456; 346 illus. (19 colored). Baltimore: Williams & Wilkins Company, 1943. Price, $8.00.

THE appearance of the war edition of this book is made possible only by the English publisher's "overcoming insuperable difficulties after repeated destruction of their works by bombing." Nazi bombs failed either to stop the printing or the efforts of the authors in revising this book. In the 5 years elapsed since the last edition, considerable revision has been required. Among the main changes are the additions to the section on endocrine defects, amplification of the symptoms and signs of respiratory disease and extensive revision of the chapter on the cardiovascular system. Of war interest is Dr. A. R. D. Adams' useful details on tropical parasites.

The author, however, has retained the rightful importance given to physical signs observed by the unaided eye in the diagnosis of disease. Dr. Chamberlain's attitude in writing each chapter before consulting standard textbooks and monographs is highly commendable, for it represents what a physician can carry in his mind. The book, therefore, is valuable to first-year clinical students in giving them the information essential in making a physical diagnosis.

J. S.

PATHOLOGICAL HISTOLOGY. By ROBERTSON F. OGILVIE, M.D., F.R.C.P. (EDIN.), Lecturer in Pathology and Assistant in Forensic Medicine, University of Edinburgh; Senior Pathologist, Royal Infirmary, Edinburgh; Pathologist to the Leith and Deaconess Hospitals, Edinburgh; Examiner in Pathology and Forensic Medicine for the Triple Qualification. Second Ed. Pp. 411; 235 photomicrographs in color. Baltimore: Williams & Wilkins Company, 1943. Price, $9.00.

THIS book retains all of the excellent features of the first edition, has many new illustrations, and new matter on pathologic changes in intestinal tract, kidneys, bones, and reproductive organs, and much has been rewritten and amplified. In spite of these additions, the book is slightly smaller and lighter in weight than the first edition.

All of the 235 photomicrographs are in color, are of superb technique, and are well chosen as representative examples of common pathologic conditions. This book is intended as a companion to a standard textbook of pathology, to aid students in studying their microscopic slides. Although the emphasis is on the clear, simple description of histologic changes, there is always a preceding brief description of gross pathology, etiology and pathogenesis. Uncommon conditions are not included.

The only criticism the Reviewer would make would be in the matter of terminology; for instance, it seems unwise to use such terms as "glycogen degeneration" and "tubular nephritis." But these are minor matters and do not detract from the usefulness of this volume in helping the student to see the common microscopic changes of disease. I. Z.

PHYSIOLOGICAL PSYCHOLOGY. By CLIFFORD T. MORGAN, Associate in Psychology, The Johns Hopkins University; Formerly Faculty Instructor in Psychology, Harvard University. Pp. 623; 176 figs. New York and London: McGraw-Hill Book Company, Inc., 1943. Price, $4.00.

GREAT advances in a field of science are made when the methods of experimentation become more simplified, more easily reproducible, and more quantitative. As the experimental facts accumulate, however, and new concepts are developed, further advances often require correlation of ideas with other fields of investigation.

This book has been written as a presentation of the known experimental facts important in the understanding of certain concepts of the physiologic mechanism of normal human and animal behavior. Of these, 3 have been stressed by the author—*internal environment*, *interaction*, and *levels of organization of function*. This has been done so well that workers in other fields, especially biochemistry, can with little difficulty determine whether certain psychologic problems fall within the realm of their experimental technics and understanding. "This book is meant to be both a textbook for under-graduates who are preparing for psychology or medicine and a reference book for graduate students and workers in psychology, physiology, and medicine." In the Reviewer's opinion, however, the revolution expected in psychology as a result of the impact of biochemistry, so often heard in psychological circles, can certainly spring from this book as its manifesto.

The difficulties of writing a textbook of this type lie chiefly in the choice between an elementary presentation of factual material and a scientific presentation from the investigator's point of view who demands an interpretation of the facts in light of the limitation of experimental procedures. The author has overcome these difficulties by presenting the elementary material of psychology, physiology and anatomy in the first part of the book, and then discussing the more advanced research, with complete bibliographic references (780), in the rest of the book. The bibliography also contains an author index whereby the page upon which that reference is made is found with the bibliographic reference. This is an extremely useful index procedure.

J. S.

PERSONAL AND COMMUNITY HEALTH. By C. E. TURNER, A.M., Sc.D., Dr.-P.H., Professor of Public Health in the Massachusetts Institute of Technology; Formerly Associate Professor of Hygiene in the Tufts College Medical and Dental Schools; Sometime Member of the Administrative Board in the School of Public Health of Harvard University and the Massachusetts Institute of Technology. Seventh ed. Pp. 585; many figs., 4 colored plates. St. Louis: C. V. Mosby Company, 1943. Price, $3.50.

THE author presents another edition of an outstanding text for health instruction of college and university levels. It incorporates recent advances in the fields of public health and medical sciences with the basic fundamentals

of each, without burdening the student with unnecessary details. The book has been developed over a period of many years of personal experience in health instruction to students of various age levels and from suggestions offered by co-workers and colleagues in the field of public health and hygiene. A book of this type could certainly be utilized advantageously in college courses in personal and community health and as a text in an introductory course in the biologic sciences. F. E.

NEW BOOKS

The Medical Clinics of North America. Chicago Number. Symposium on Cardiovascular Diseases. Pp. 289; 37 figs.; 7 tables. Philadelphia: W. B. Saunders Company. Price, $16.00 per year.

The Sexual Glands of the Male. By OSWALD SWINNEY LOWSLEY, A.B., M.D., F.A.C.S., Collaborators: FRANK HINMAN, A.B., M.D., F.A.C.S., DONALD R. SMITH, A.B., M.D., and ROBERT GUTIERREZ, A.B., M.D., F.A.C.S. Reprinted from Oxford Loose-Leaf Urology. Pp. 619; 4 tables; 59 figs. New York: Oxford University Press. Price, $10.00.

On the Influence of Trades, Professions, and Occupations in the United States, in the Production of Disease. (Reprinted from Transactions of the Medical Society of the State of New York, Vol. III, 1837, pp. 91–150.) By BENJAMIN W. MCCREADY, M.D. Introductory Essay by GENEVIEVE MILLER, M.A. (Publications of the Institute of the History of Medicine, The Johns Hopkins University. Fourth Series: Bibliotheca Medica Americana, Vol. 4.) Pp. 127. Baltimore: The Johns Hopkins Press. Price, $1.75.

Pathology and Therapy of Rheumatic Fever. By LEOPOLD LICHTWITZ, M.D., Lately, Chief of the Medical Division of the Montefiore Hospital, and Clinical Professor of Medicine, Columbia University, New York City. Foreword by WILLIAM J. MALONEY, M.D., LL.D., F.R.S. (EDIN.), Consulting Neurologist to the City Hospital; Formerly Professor of Nervous and Mental Diseases, Fordham University, New York City. Edited by MAJOR WILLIAM CHESTER, M.C. Pp. 211; 69 figs. New York: Grune & Stratton, Inc., 1944. Price, $4.75.

The Health of Children in Occupied Europe. Published by the International Labour Office. Pp. 37; 2 tables. Montreal, Canada, 1943. Price, 25c (one shilling).

A small pamphlet studying "The effects of the war on the health of the children (in occupied Europe). . . . Because of the difficulty of collecting precise and reliable information . . . the data quoted are fragmentary and serve only to illustrate the state of affairs."—Introduction.

Office Treatment of the Nose, Throat and Ear. By A. R. HOLLENDER, M.Sc., M.D., F.A.C.S., Associate Professor of Laryngology, Rhinology and Otology, University of Illinois College of Medicine; Otolaryngologist, Research and Educational Hospitals, Chicago, Ill. Pp. 480; 33 figs. Chicago: The Year Book Publishers, Inc., 1943. Price, $5.00.

Physical Biochemistry. By HENRY B. BULL, PH.D., Associate Professor of Physiological Chemistry, Medical School of Northwestern University. Pp. 347; 93 figs.; 44 tables. London: Chapman & Hall, Ltd.; New York: John Wiley & Sons, Inc., 1943. Price, $3.75.

The Permeability of Natural Membranes. By HUGH DAVSON, D.Sc., Associate Professor of Physiology at Dalhousie University, Canada; formerly Demonstrator in Biophysics and Beit Memorial Fellow, University College, London; and JAMES FREDERIC DANIELLI, D.Sc., A.I.C., Beit Memorial Research Fellow and Fellow of St. John's College, Cambridge, England. Foreword by E. NEWTON HARVEY, Professor of Physiology in Princeton University. Pp. 361; 73 figs.; 72 tables. Cambridge: At the University Press; New York: The Macmillan Company, 1943. Price, $4.75.

A Catalogue of the Medieval and Renaissance Manuscripts and Incunabula in the Boston Medical Library. Compiled by JAMES F. BALLARD, Director, Boston Medical Library. Pp. 246; 23 figs. Boston: Privately printed.

Human Constitution in Clinical Medicine. By GEORGE DRAPER, M.D., Associate Professor of Clinical Medicine, College of Physicians and Surgeons, Columbia University, and Associate Attending Physician, Presbyterian Hospital, New York City; C. W. DUPERTUIS, PH.D., Physical Anthropologist, Constitution Clinic, Presbyterian Hospital, New York City; and J. L. CAUGHEY, JR., M.D., MED.SCI.D., Associate in Medicine, College of Physicians and Surgeons, Columbia University; Assistant Physician, Presbyterian Hospital, New York City. Pp. 273; 29 figs.; 30 tables. New York and London: Paul B. Hoeber, Inc. Price, $4.00.

Health and Hygiene. A Comprehensive Study of Disease Prevention and Health Promotion. By LLOYD ACKERMAN, Western Reserve University. Pp. 895; 59 figs.; 27 tables. Lancaster, Pa.: The Jaques Cattell Press, 1943. Price, $5.00.

The British Encyclopædia of Medical Practice including Medicine, Surgery, Obstetrics, Gynecology, and Other Special Subjects. *Medical Progress,* 1943 (Pp. 382); *Cumulative Supplement,* 1943 (Pp. 342; 5 figs.). Under the General Editorship of SIR HUMPHRY ROLLESTON, BT., G.C.V.O., K.C.B., M.D., D.Sc., D.C.L., LL.D., Emeritus Regius Professor of Physic, Cambridge; Sometime President of the Royal College of Physicians of London. London, Eng., and Toronto, Can.: Butterworth & Co. (Publishers), Ltd., 1943.

Soviet Health Care in Peace and War. By ROSE MAURER. The American Russian Institute for Cultural Relations With the Soviet Union, Inc. Pp. 48; a few illus. New York: American Russian Institute. Price, 10c.

An informative pamphlet on the remarkable medical achievements of Soviet Russia in recent years, written to illustrat the application of the principle that health is a community affair.—E. K.

NEW EDITIONS

An Outline of General Physiology. By L. V. HEILBRUNN, Professor of Zoölogy in the University of Pennsylvania. Second ed. Pp. 478; 135 illus. Philadelphia and London: W. B. Saunders Company, 1943. Price, $6.00.

Urology for Nurses. By OSWALD SWINNEY LOWSLEY, M.D., F.A.C.S., Director of the Department of Urology (James Buchanan Brady Foundation) of the New York Hospital; and THOMAS JOSEPH KIRWIN, M.D., F.A.C.S., Attending Urologist of the Department of Urology (James Buchanan Brady Foundation) of the New York Hospital. New Printing. Pp. 493; 108 illus. Philadelphia: J. B. Lippincott Company, 1943. Price, $3.00.

Chemistry of Organic Medicinal Products. By GLEN L. JENKINS, Dean and Professor of Pharmaceutical Chemistry, School of Pharmacy, Purdue University; and WALTER H. HARTUNG, Professor of Pharmaceutical Chemistry, School of Pharmacy, The University of Maryland. Second ed. Pp. 675; 71 tables; many small figs. New York: John Wiley & Sons, Inc., 1943. Price, $6.50.

Recent Advances in Medicine. By G. E. BEAUMONT, M.A., D.M. (OXON.), F.R.C.P., D.P.H. (LOND.), Physician to the Middlesex Hospital; Physician to the Hospital for Consumption and Diseases of the Chest, Brompton; Lecturer in Medicine, Middlesex Hospital Medical School; Formerly Censor Royal College of Physicians, London; and E. C. DODDS, M.V.O., D.Sc., PH.D., M.D., F.R.C.P., F.I.C., F.R.S. (EDIN.), F.R.S., Courtauld Professor of Biochemistry in the University of London; Director of Courtauld Institute of Biochemistry, Middlesex Hospital; Pathologist to the Royal National Orthopædic Hospital. Eleventh ed. Pp. 412; 43 figs.; many tables. Philadelphia: The Blakiston Company, 1943. Price, $5.50.

A Text-book of Histology, Arranged Upon an Embryological Basis by J. LEWIS BREMER, M.D., Hersey Professor of Anatomy, Harvard University. Rewritten by HAROLD L. WEATHERFORD, PH.D., Assistant Professor of Anatomy, Harvard University. Sixth ed. of "Lewis and Stöhr." Pp. 723; 598 illus. Philadelphia: The Blakiston Company, 1944. Price, $7.00.

Essentials of Dermatology. By NORMAN TOBIAS, M.D., Senior Instructor in Dermatology, St. Louis University; Assistant Dermatologist, Firmin Desloge and St. Mary's Hospitals; Visiting Dermatologist, St. Louis City Sanitarium and Isolation Hospital; Fellow, American Academy of Dermatology and Syphilology; Diplomate, American Board of Dermatology and Syphilology. Second ed. Pp. 497; 143 figs. Philadelphia, London, Montreal: J. B. Lippincott Company. Price, $4.75.

Applied Dietetics. The Planning and Teaching of Normal and Therapeutic Diets. By FRANCES STERN, Chief of Frances Stern Food Clinic, The Boston Dispensary; Assistant in Medicine, Tufts College Medical School; Special Instructor in Dietetics in Social Service, Simmons College, The School of Social Work; Associate in Nutrition, Simmons College, School of Home Economics. Second ed. Pp. 265; a few figs.; 57 tables. Baltimore: The Williams & Wilkins Company, 1943. Price, $4.00.

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